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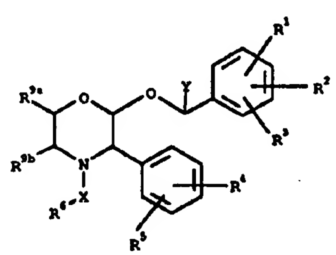

(I)

(57) Abstract

The present invention relates to compounds of formula (I), wherein R^1 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6} alkenyl, C_{2-6} alkynyl or C_{1-4} alkyl substituted by C_{1-4} alkoxy, where R^a and R^b are hydrogen or C_{1-4} alkyl; R^2 is hydrogen, halogen, C_{1-6} alkyl, C_{1-6} alkoxy substituted by C_{1-4} alkoxy or CF_3; R^3 is hydrogen, halogen or CF_3; R^4 is selected from the definitions of R^1; R^5 is selected from the definitions of R^2; R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C_{1-4} alkyl group, and optionally substituted by an aminoalkyl group; R^{9a} and R^{9b} are hydrogen or C_{1-4} alkyl, or R^{9a} and R^{9b} are joined to form a C_{5-7} ring; X is C_{1-4} alkylene optionally substituted by oxo; and Y is a C_{1-4} alkyl group optionally substituted by hydroxyl; with the proviso that if Y is C_{1-4} alkyl, R^6 is substituted at least by an aminoalkyl group; and pharmaceutically acceptable salts and prodrugs thereof. The compounds are of particular use in the treatment of pain, inflammation, migraine and emesis.

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SUBSTITUTED MORPHOLINE DERIVATIVES AND THEIR USE AS THERAPEUTIC AGENTS

This invention relates to a class of aromatic compounds which are useful as tachykinin antagonists. More particularly, the compounds of the invention contain an amine-substituted azo-heterocyclic moiety.

The tachykinins are a group of naturally occurring peptides found widely distributed throughout mammalian tissues, both within the central nervous system and in peripheral nervous and circulatory systems.

The tachykinins are distinguished by a conserved carboxyl-terminal sequence:

Phe-X-Gly-Leu-Met-NH_2

At present, there are three known mammalian tachykinins referred to as substance P, neurokinin A (NKA, substance K, neuromedin L) and neurokinin B (NKB, neuromedin K) (for review see J.E. Maggio, *Peptides* (1985) 6(suppl. 3), 237-242). The current nomenclature designates the three tachykinin receptors mediating the biological actions of substance P, NKA and NKB as the NK_1, NK_2 and NK_3 receptors, respectively.

Evidence for the usefulness of tachykinin receptor antagonists in pain, headache, especially migraine, Alzheimer's disease, multiple sclerosis, attenuation of morphine withdrawal, cardiovascular changes, oedema, such as oedema caused by thermal injury, chronic inflammatory diseases such as rheumatoid arthritis, asthma/bronchial hyperreactivity and other respiratory diseases including allergic rhinitis, inflammatory diseases of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases, proliferative vitreoretinopathy, irritable bowel syndrome and disorders of bladder function including cystitis and bladder detruser hyper-reflexia is reviewed in "Tachykinin Receptors and Tachykinin

Receptor Antagonists", C.A. Maggi, R. Patacchini, P. Rovero and A. Giachetti, *J. Auton. Pharmacol.* (1993) 13, 23-93.

For instance, substance P is believed inter alia to be involved in the neurotransmission of pain sensations [Otsuka *et al*, "Role of Substance P as a Sensory Transmitter in Spinal Cord and Sympathetic Ganglia" in *1982 Substance P in the Nervous System*, Ciba Foundation Symposium 91, 13-34 (published by Pitman) and Otsuka and Yanagisawa, "Does Substance P Act as a Pain Transmitter?" *TIPS* (1987) 8, 506-510], specifically in the transmission of pain in migraine (B.E.B. Sandberg *et al, J. Med Chem*, (1982) 25, 1009) and in arthritis [Levine *et al Science* (1984) 226, 547-549]. Tachykinins have also been implicated in gastrointestinal (GI) disorders and diseases of the GI tract such as inflammatory bowel disease [Mantyh *et al Neuroscience* (1988) 25(3), 817-37 and D. Regoli in *"Trends in Cluster Headache"* Ed. Sicuteri *et al* Elsevier Scientific Publishers, Amsterdam (1987) page 85)] and emesis [F. D. Tattersall *et al, Eur. J. Pharmacol.*, (1993) 250, R5-R6]. It is also hypothesised that there is a neurogenic mechanism for arthritis in which substance P may play a role [Kidd *et al* "A Neurogenic Mechanism for Symmetrical Arthritis" in *The Lancet*, 11 November 1989 and Grönblad *et al*, "Neuropeptides in Synovium of Patients with Rheumatoid Arthritis and Osteoarthritis" in *J. Rheumatol.* (1988) 15(12), 1807-10]. Therefore, substance P is believed to be involved in the inflammatory response in diseases such as rheumatoid arthritis and osteoarthritis, and fibrositis [O'Byrne *et al, Arthritis and Rheumatism* (1990) 33, 1023-8]. Other disease areas where tachykinin antagonists are believed to be useful are allergic conditions [Hamelet *et al, Can. J. Pharmacol. Physiol.* (1988) 66, 1361-7], immunoregulation [Lotz *et al, Science* (1988) 241, 1218-21 and Kimball *et al, J. Immunol.* (1988) 141(10), 3564-9] vasodilation, bronchospasm, reflex or neuronal control of the viscera [Mantyh *et al, PNAS* (1988) 85, 3235-9] and, possibly by arresting or slowing

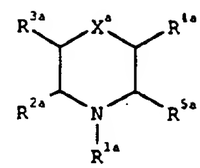
ß-amyloid-mediated neurodegenerative changes [Yankner *et al, Science* (1990) 250, 279-82] in senile dementia of the Alzheimer type, Alzheimer's disease and Down's Syndrome.

Tachykinin antagonists may also be useful in the treatment of small cell carcinomas, in particular small cell lung cancer (SCLC) [Langdon *et al, Cancer Research* (1992) 52, 4554-7].

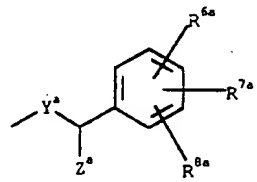
Substance P may also play a role in demyelinating diseases such as multiple sclerosis and amyotrophic lateral sclerosis [J. Luber-Narod *et al*, poster *C.I.N.P. XVIIIth Congress*, 28th June-2nd July 1992], and in disorders of bladder function such as bladder detrusor hyper-reflexia (*Lancet*, 16th May 1992, 1239).

It has furthermore been suggested that tachykinins have utility in the following disorders: depression, dysthymic disorders, chronic obstructive airways disease, hypersensitivity disorders such as poison ivy, vasospastic diseases such as angina and Reynauld's disease, fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis, reflex sympathetic dystrophy such as shoulder/hand syndrome, addiction disorders such as alcoholism, stress related somatic disorders, neuropathy, neuralgia, disorders related to immune enhancement or suppression such as systemic lupus erythmatosus (European patent specification no. 0 436 334), ophthalmic disease such as conjuctivitis, vernal conjunctivitis, and the like, and cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis (European patent specification no. 0 394 989).

European patent specification no. 0 577 394 (published 5th January 1994) discloses morpholine and thiomorpholine tachykinin receptor antagonists of the general formula



wherein R^{1a} is a large variety of substituents;
R^{2a} and R^{3a} are *inter alia* hydrogen;
R^{4a} is *inter alia*



;

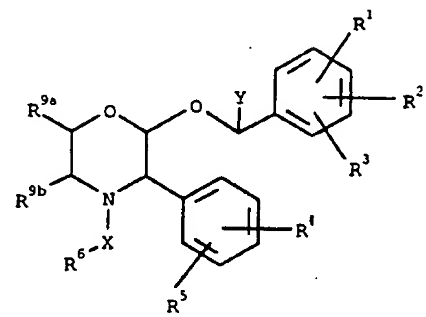
R^{5a} is *inter alia* optionally substituted phenyl;
R^{6a}, R^{7a} and R^{8a} are a variety of substituents;
X^a is O, S, SO or SO_2;
Y^a is *inter alia* O; and
Z^a is hydrogen or C_{1-4}alkyl.

We have now found a further class of non-peptides which are potent antagonists of tachykinins, especially of substance P.

It is desirable that compounds may be administered orally and by injection. Compounds have now been discovered which act as potent non-peptide tachykinin antagonists and which, by virtue of their advantageous aqueous solubility, are particularly easily formulated for administration by both the oral and injection routes, for example in aqueous media.

Furthermore, the compounds of the present invention possess a particularly advantageous profile of activity having potent antagonist activity at the NK_1 receptor and a long duration of action. The compounds of the present invention, and in particular their pharmaceutically acceptable acid addition salts, are also particularly suited to a wide variety of pharmaceutical formulations by virtue of their stability.

The present invention provides compounds of the formula (I):



(I)

wherein

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^3 is hydrogen, halogen or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C_{1-4}alkyl group, and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo; and

Y is a C_{1-4}alkyl group optionally substituted by a hydroxyl group;

with the proviso that if Y is C_{1-4}alkyl, R^6 is substituted at least by a group of formula ZNR^7R^8 as defined above;

and pharmaceutically acceptable salts and prodrugs thereof.

Certain particularly apt compounds of the present invention include those wherein R^1 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halo or CF_3.

Most aptly R^2 is hydrogen, C_{1-4}alkyl, C_{1-4}alkoxy, halogen or CF_3.

Most aptly R^3 is hydrogen, fluorine, chlorine or CF_3.

Favourably R^1 is fluorine, chlorine or CF_3.

Favourably R^2 is hydrogen, fluorine, chlorine or CF_3.

Favourably R^3 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^1 and R^2 are in the 3 and 5 positions of the phenyl ring.

More preferably R^1 is 3-fluoro or 3-CF_3.

More preferably R^2 is 5-fluoro or 5-CF_3.

More preferably R^3 is hydrogen.

Most preferably R^1 is 3-F or 3-CF_3, R^2 is 5-CF_3 and R^3 is hydrogen.

Most aptly R^4 is hydrogen.

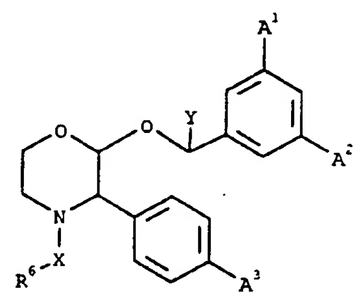
Most aptly R^5 is hydrogen, fluorine, chlorine or CF_3.

Preferably R^4 is hydrogen and R^5 is hydrogen or 4-fluoro.

Most aptly R^{9a} and R^{9b} are each independently hydrogen or methyl.

Preferably R^{9a} is hydrogen. Preferably R^{9b} is hydrogen. Most preferably R^{9a} and R^{9b} are both hydrogen.

From the foregoing it will be appreciated that a particularly apt sub-group of compounds of this invention are those of the formula (Ia) and pharmaceutically acceptable salts and prodrugs thereof:



(Ia)

wherein A^1 is fluorine or CF_3;

A^2 is fluorine or CF_3;

A^3 is fluorine or hydrogen;

and X, Y and R^6 are as defined in relation to formula (I).

According to a second or further aspect of the present invention, a preferred class of compound of formula (I) or (Ia) is that wherein Y represents a C_{1-4}alkyl group substituted by a hydroxy group; or a pharmaceutically acceptable salt or prodrug thereof.

According to a further or alternative aspect of the present invention, another preferred class of compound of formula (I) or (Ia) is that wherein Y represents a C_{1-4}alkyl group, with the proviso that R^6 is substituted at least by a group of the formula ZNR^7R^8 as defined above; or a pharmaceutically acceptable salt or prodrug thereof.

According to another aspect of the present invention, a further preferred class of compound of formula (I) or (Ia) is that wherein

Y represents a C_{1-4}alkyl group; and

R^6 represesents a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a hydroxy group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second

nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

or a pharmaceutically acceptable salt or prodrug thereof.

According to yet another aspect of the present invention, a preferred class of compounds of formula (I) or (Ia) is that wherein

Y represents a C_{1-4}alkyl group; and

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen or C_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl, R^8 is hydrogen or C_{1-4}alkyl or C_{2-4}alkyl substituted by C_{1-4}alkoxy, hydroxyl or a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by a hydroxy group, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^C moiety where R^C is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

or a pharmaceutically acceptable salt or prodrug thereof.

According to a further aspect of the present invention, another preferred class of compound of formula (I) or (Ia) is that wherein

Y represents a C_{1-4}alkyl group substituted by a hydroxyl group; and

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen or C_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl, R^8 is hydrogen or C_{1-4}alkyl or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

or a pharmaceutically acceptable salt or prodrug thereof.

According to another aspect of the present invention, a further preferred class of compound of formula (I) or (Ia) is that wherein

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O or =S and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkyl;

R^7 is hydrogen or C_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl, R^8 is hydrogen or C_{1-4}alkyl or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an

oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or Z, R^7 and the nitrogen atom to which that are attached form a heteroaliphatic ring to 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

or a pharmaceutically acceptable salt or prodrug thereof.

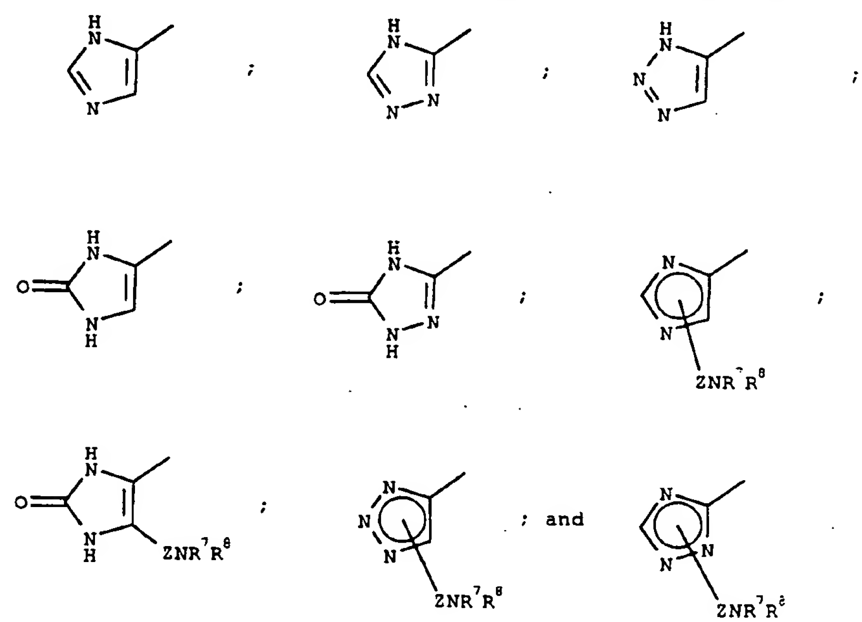
A preferred group Y for compounds of the formulae (I) or (Ia) is the CH_2OH group.

Another preferred group Y for compounds of the formulae (I) or (Ia) is the CH_3 group.

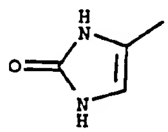
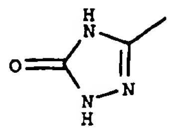
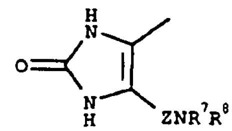
Particularly apt values for X for compounds of the formulae (I) or (Ia) include CH_2, $CH(CH_3)$ and CH_2CH_2 of which the CH_2 group is preferred.

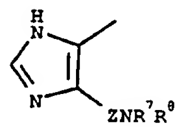
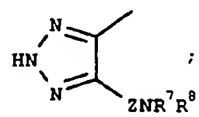
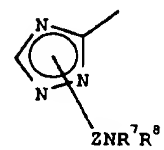
Favourably R^6 is a 5-membered ring.

In particular, R^6 may, bearing in mind the proviso in the definition of formula (I), represent a heterocyclic ring selected from:

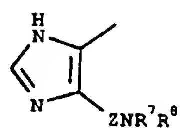
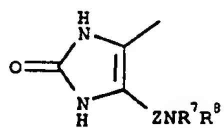
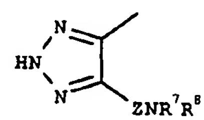


Particularly preferred heterocyclic rings represented by R^6 are selected from:

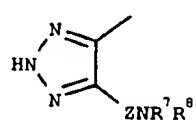
 ;  ;  ;

 ;  ; and  .

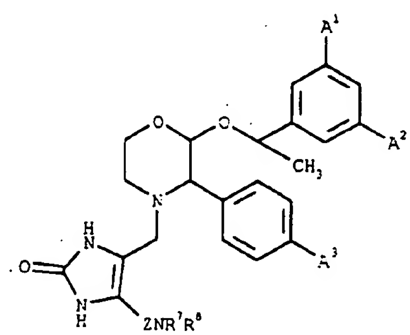
Most especially, R^6 may represent a heterocyclic ring selected from:

 ;  ; and  .

A particularly preferred heterocyclic ring represented by R^6 is:

 .

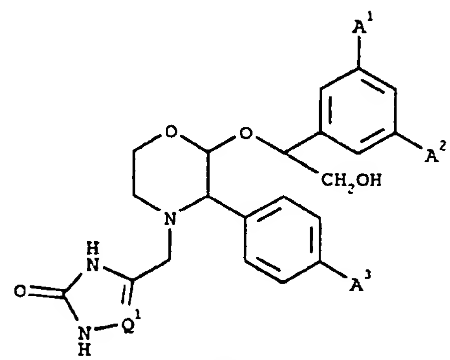
One favoured group of compounds of this invention are of the formula (Ib) and pharmaceutically acceptable salts and prodrugs thereof:



(Ib)

wherein A^1, A^2 and A^3 are defined in relation to formula (Ia) and wherein Z, R^7 and R^8 are as defined in relation to formula (I).

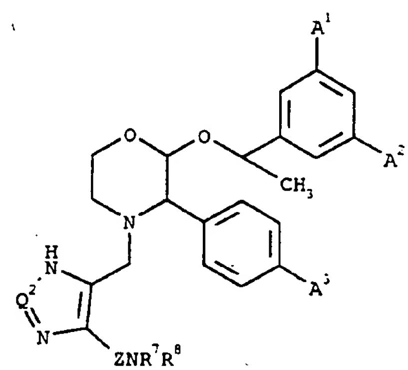
A further favoured group of compounds of the present invention are of the formula (Ic) and pharmaceutically acceptable salts and prodrugs thereof:



(Ic)

wherein A^1, A^2 and A^3 are as defined in relation to formula (Ia) and Q^1 is CH or N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in relation to formula (I).

Another favoured group of compounds of the present invention are of the formula (Id) and pharmaceutically acceptable salts and prodrugs thereof:



(Id)

wherein A^1, A^2 and A^3 are defined in relation to formula (Ia), Q^2 is CH or N and Z, R^7 and R^8 are as defined in relation to formula (I).

With respect to compounds of the formulae (I), (Ia), (Ib), (Ic) and (Id), Z may be a linear, branched or cyclic group. Favourably Z contains 1 to 4 carbon atoms and most favourably 1 or 2 carbon atoms. A particularly favourable group Z is CH_2.

With respect to compounds of the formulae (I), (Ia), (Ib), (Ic) and (Id), R^7 may aptly be a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, R^8 may aptly be a C_{1-4}alkyl group or a C_{1-4}alkyl group substituted by a hydroxyl or C_{1-2}alkoxy group, or R^7 and R^8 may be linked so that, together with the nitrogen atom to which they are attached, they form an azetidinyl, pyrrolidinyl, piperidyl, morpholino, thiomorpholino, piperazino or piperazino group substituted on the nitrogen atom by a C_{1-4}alkyl group or a C_{2-4}alkyl group substituted by a hydroxy or C_{1-2}alkoxy group.

Where the group NR^7R^8 represents a heteroaliphatic ring of 4 to 7 ring atoms and said ring contains a double bond, a particularly preferred group is 3-pyrroline.

Where the group NR^7R^8 represents a non-aromatic azabicyclic ring system, such a system may contain between 6 and 12, and preferably between 7 and 10, ring atoms. Suitable rings include 5-azabicyclo[2.1.1]hexyl, 5-azabicyclo[2.2.1]heptyl, 6-azabicyclo[3.2.1]octyl, 2-azabicyclo[2.2.2]octyl, 6-azabicyclo[3.2.2]nonyl, 6-azabicyclo[3.3.1]nonyl, 6-azabicyclo[3.2.2]decyl, 7-azabicyclo[4.3.1]decyl, 7-azabicyclo[4.4.1]undecyl and 8-azabicyclo[5.4.1]dodecyl, especially 5-azabicyclo[2.2.1]heptyl and 6-azabicyclo[3.2.1]octyl.

Where R^8 represents a C_{2-4}alkyl group substituted by a 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S, suitable rings include pyrrolidino, piperidino, piperazino, morpholino, or thiomorpholino. Particularly preferred are nitrogen containing heteroaliphatic rings, especially pyrrolidino and morpholino rings.

Particularly suitable moieties ZNR^7R^8 include those wherein Z is CH_2 or CH_2CH_2 and NR^7R^8 is amino, methylamino, dimethylamino, diethylamino, azetidinyl, pyrrolidino and morpholino.

Further preferred moieties represented by ZNR^7R^8 are those wherein Z is CH_2 or CH_2CH_2, R^7 represents hydrogen, C_{1-4}alkyl or C_{3-6}cycloalkyl and R^8 is C_{2-4}alkyl substituted by one or two substituents selected from hydroxy, C_{1-2}alkoxy, azetidinyl, pyrrolidino, piperidino, morpholino or thiomorpholino.

In particular, Z is preferably CH_2 and NR^7R^8 is preferably dimethylamino, azetidinyl or pyrrolidino, especially dimethylamino.

With regard to compounds of the formulae (Ia), (Ib), (Ic) and (Id), A^1 is preferably fluorine or CF_3; A^2 is preferably CF_3; and A^3 is preferably fluorine.

As used herein, the term "alkyl" or "alkoxy" as a group or part of a group means that the group is straight or branched. Examples of suitable alkyl groups include methyl, ethyl, n-propyl, i-propyl, n-butyl, s-butyl and t-butyl. Examples of suitable alkoxy groups include methoxy, ethoxy, n-propoxy, i-propoxy, n-butoxy, s-butoxy and t-butoxy.

The cycloalkyl groups referred to herein may represent, for example, cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl. A suitable cycloalkylalkyl group may be, for example, cyclopropylmethyl.

As used herein, the terms "alkenyl" and "alkynyl" as a group or part of a group means that the group is straight or branched. Examples of suitable alkenyl groups include vinyl and allyl. A suitable alkynyl group is propargyl.

When used herein the term halogen means fluorine, chlorine, bromine and iodine. The most apt halogens are fluorine and chlorine of which fluorine is preferred.

Specific compounds within the scope of this invention include:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2,3-dihydro-5-(N,N-dimethylamino)methyl-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

4-(2,3-dihydro-5-(N,N-dimethylamino)methyl-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)morpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(4-hydroxypiperidino)methyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(2,3-dihydro-5-morpholinomethyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-morpholinomethyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

4-(5-azetidinylmethyl-2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(N-methylpiperazinyl)methyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(N-(2-morpholinoethyl)aminomethyl)-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-(N-(2-pyrrolidinoethyl)aminomethyl)-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino) methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-(N'-methylaminoethyl)-1,2,4-triazol-3-yl)methylmorpholine;

and pharmaceutically acceptable salts or prodrugs thereof.

Further preferred compounds within the scope of the present invention include:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(N-methylaminomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-aminomethyl)-1,2,3-triazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-pyrrolidinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-(azetidinylmethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)morpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(5-(pyrrolidinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(5-(morpholinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-(N,N-dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(N'-methylpiperazinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-(1-(2-pyrrolidinoethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(2-pyrrolidinoethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(morpholinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-azetidinylmethyl)-1,2,3-triazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(pyrrolinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(bis(methoxyethyl)aminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-chloro-5-morpholinomethyl-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N-(2,2-dimethoxyethyl)-N-methylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-(2-methoxyethyl)-N-methyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-isopropyl-N-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-cyclopropyl-N-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N,N-dibutylaminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N,N-diisopropylaminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

and pharmaceutically acceptable salts or prodrugs thereof.

Yet further preferred compounds within the scope of the present invention include:

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine;

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;

4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;

4-(2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl) morpholine;

4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl) morpholine;

4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)-3-(S)-phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;

4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine;

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)-3-(S)-phenylmethylmorpholine;

3-(S)-phenyl-4-(1,2,4-triazol-3-yl)-2-(R)-(1-(S)-3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;

and pharmaceutically acceptable salts or prodrugs thereof.

Further preferred compounds within the scope of the present invention are described in the Examples described herein.

In a further aspect of the present invention, the compounds of formula (I) will preferably be prepared in the form of a pharmaceutically acceptable salt, especially an acid addition salt.

For use in medicine, the salts of the compounds of formula (I) will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable acid such as hydrochloric acid, fumaric acid, p-toluenesulphonic acid, maleic acid, succinic acid, acetic acid, citric acid, tartaric acid, carbonic acid, phosphoric acid or sulphuric acid. Salts of amine groups may also comprise quaternary ammonium salts in which the amino nitrogen atom carries a suitable organic group such as an alkyl, alkenyl, alkynyl or aralkyl moiety. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include metal salts such as alkali metal salts, e.g. sodium or potassium salts; and alkaline earth metal salts, e.g. calcium or magnesium salts.

The present invention includes within its scope prodrugs of the compounds of formula (I) above. In general, such prodrugs will be functional derivatives of the compounds of formula (I) which are readily convertible *in vivo* into the required compound of formula (I). Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

A prodrug may be a pharmacologically inactive derivative of a biologically active substance (the "parent drug" or "parent molecule") that requires transformation within the body in order to release the active drug, and that has improved delivery properties over the parent drug molecule. The transformation *in vivo* may be, for example, as the result of some metabolic process, such as chemical or enzymatic hydrolysis of a carboxylic, phosphoric or sulphate ester, or reduction or oxidation of a susceptible functionality.

Thus, for example, certain preferred prodrugs may not be antagonists of tachykinin, particularly substance P, activity to any significant extent (or not at all). Such compounds, however, are still advantageous in treating the various conditions described herein, especially where an injectable formulation is preferred.

The advantages of a prodrug may lie in its physical properties, such as enhanced water solubility for parenteral administration compared with the parent drug, or it may enhance absorption from the digestive tract, or it may enhance drug stability for long-term storage. Ideally a prodrug will improve the overall efficacy of a parent drug, for example, through the reduction of toxicity and unwanted effects of drugs by controlling their absorption, blood levels, metabolism, distribution and cellular uptake.

A particularly preferred class of prodrugs of the compounds of the present invention is that wherein the hydroxyl moiety of the group Y in formula (I) (when Y if C_{1-4}alkyl substituted by hydroxyl) is derivatized.

It will be appreciated that a further class of prodrugs of the compounds of the present invention is that wherein the heterocyclic group represented by R^6 in formula (I) is derivatized, or alternatively, wherein both the hydroxyl moiety of the group Y (when Y is C_{1-4}alkyl substituted by hydroxyl) and the heterocyclic group represented by R^6 in formula (I) are derivatized.

Suitable prodrug derivatives include:

(a) $-(CHR^{10})_n-PO(OH)O^-.M^+$;

(b) $-(CHR^{10})_n-PO(O^-)_2.2M^+$;

(c) $-(CHR^{10})_n-PO(O^-)_2.D^{2+}$;

(d) $-(CHR^{10})_n-SO_3^-.M^+$;

(e) $-COCH_2CH_2CO_2^-.M^+$;

(f) -COH;

(g) $-CO(CH_2)_nN(R^{10})_2$; and

(h) $-(CH(R^{10})O)_n-COR^{11}$,

wherein

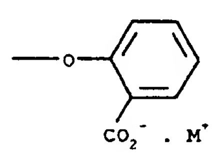
n is zero or 1;

M^+ is a pharmaceutically acceptable monovalent counterion;

D^{2+} is a pharmaceutically acceptable divalent counterion;

R^{10} is hydrogen or C_{1-3}alkyl; and

R^{11} is a group selected from $-O(CH_2)_2NH_3^+.M^-$; $-O(CH_2)_2NH_2(R^{12})^+.M^-$; $-OCH_2CO_2^-.M^+$; $-OCH(CO_2^-.M^+)CH_2CO_2^-.M^+$; $-OCH_2CH(NH_3^+)CO_2^-$; $-OC(CO_2^-.M^+)(CH_2CO_2^-.M^+)_2$; and



,

in which M^- is a pharmaceutically acceptable monovalent counterion, and R^{12} is hydrogen, C_{1-4}alkyl or C_{2-4}alkyl substituted by a hydroxyl or C_{1-4}alkoxy group.

Particularly preferred prodrug derivatives are:

(a) $-(CHR^{10})_n-PO(OH)O^-.M^+$;

(b) $-(CHR^{10})_n-PO(O^-)_2.2M^+$;

(c) $-(CHR^{10})_n-PO(O^-)_2.D^{2+}$;

especially where n is zero.

The term "parent molecule", "parent compound" or "parent drug" refers to the biologically active entity that is released via enzymatic action of a metabolic or catabolic process, or via a chemical process following administration of the prodrug. The parent compound may also be the starting material for the preparation of its corresponding prodrug.

While all of the usual routes of administration are useful with the above prodrugs, the preferred routes of administration are oral and intravenous. After gastrointestinal absorption or intravenous administration, the prodrugs are hydrolyzed or otherwise cleaved *in vivo* to the corresponding parent compounds of formula (I), or a pharmaceutically acceptable salt thereof. Since the parent compounds may less than optimally soluble in aqueous solutions, the above prodrugs provide a distinct advantage by virtue of their relatively enhanced aqueous solubility.

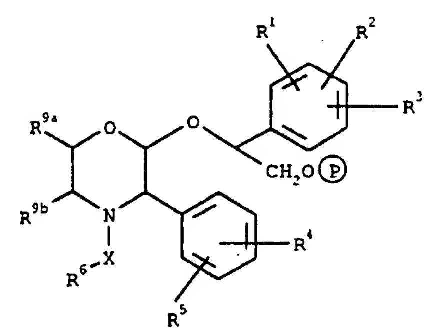
Examples of negative monovalent counterions defined herein as "M^-" include acetate, adipate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, citrate, ethanesulfonate, fumarate, hemisulfate, 2-hydroxyethylsulfonate, heptanoate, hexanoate, hydrochloride, hydrobromide, hydroiodide, lactate, malate, maleate, methanesulfonate, 2-naphthalenesulfonate, oxalate, pamoate, persulfate, picrate, pivalate, propionate, salicylate, stearate, succinate, sulfate, tartrate, tosylate (p-toluenesulfonate), and undecanoate.

Base salts (which are pharmaceutically acceptable monovalent cations defined herein as "M^+" or pharmaceutically acceptable divalent cations defined herein as "D^{2+}", if appropriate) include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as aluminium, calcium and magnesium salts, salts with organic bases such as dicyclohexylamine salts, N-methyl-D-glucamine, and salts with amino acids such as arginine, lysine, ornithine, and so forth. If M^+ is a monovalent cation, it is recognised that if the definition $2M^+$ is present, each

of M^+ may be the same or different. In addition, it is similarly recognised that if the definition $2M^+$ is present, a divalent cation D^{2+} may instead be present. Also, the basic nitrogen-containing groups may be quaternized with such agents as: lower alkyl halides, such as methyl, ethyl, propyl, and butyl chlorides, bromides and iodides; dialkyl sulfates like dimethyl, diethyl and dibutyl; diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; aralkyl halides like benzyl bromide and others. The non-toxic physiologically acceptable salts are preferred, although other salts are also useful, such as in isolating or purifying the product.

The salts may be formed by conventional means, such as by reacting the free base form of the product with one or more equivalents of the appropriate acid in a solvent or medium in which the salt is insoluble, or in a solvent such as water which is removed *in vacuo* or by freeze drying or by exchanging the anions of an existing salt for another anion on a suitable ion exchange resin.

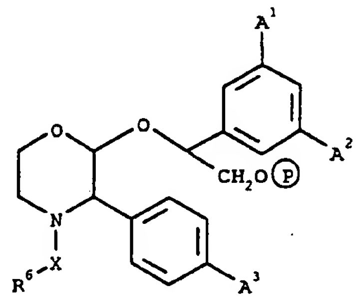
A particularly preferred sub-class of prodrugs of the compounds of the present invention is that defined by the formula (Ie) and pharmaceutically acceptable salts thereof:



(Ie)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b} and X are as defined in relation to formula (I) and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$.

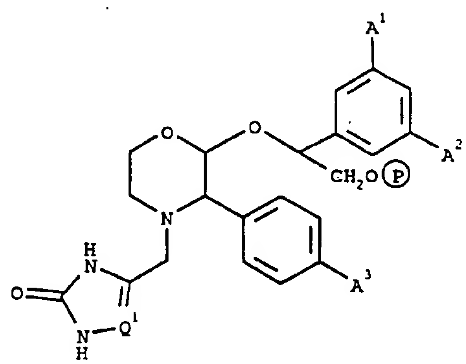
Another preferred sub-class of prodrugs of the compounds of the present invention is that defined by the formula (If) and pharmaceutically acceptable salts thereof:



(If)

wherein A^1, A^2 and A^3 are as defined in relation to formula (Ia), X and R^6 are as defined in relation to formula (I), and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$.

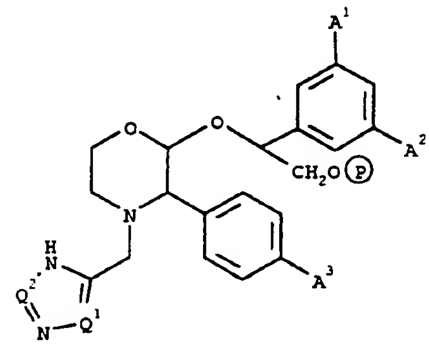
An especially preferred sub-group of prodrugs of the compounds of the present invention is that defined by formula (Ig) and pharmaceutically acceptable salts thereof:



(Ig)

wherein A^1, A^2 and A^3 are as defined in relation to formula (Ia), Q^1 is as defined in relation to formula (Ic) and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$.

A yet further preferred sub-group of prodrugs of the compounds of the present invention is that defined by formula (Ih) and pharmaceutically acceptable salts thereof:



(Ih)

wherein A^1, A^2 and A^3 are as defined in relation to formula (Ia), Q^1 and Q^2 are as defined in relation to formulae (Ic) and (Id), respectively, and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$.

Specific prodrug derivatives within the scope of this invention include:

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine;

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;

4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-3-fluoro-5-(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-phenylmorpholine;

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-phenylmorpholine;

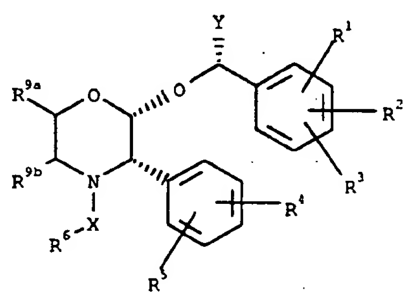
and pharmaceutically acceptable salts thereof.

With regard to compounds of the formulae (If), (Ig) and (Ih), A^1 is preferably fluorine or CF_3; A^2 is preferably CF_3; and A^3 is preferably fluorine.

The present invention includes within its scope solvates of the compounds of formula (I) and salts thereof, for example, hydrates.

The compounds according to the invention have at least three asymmetric centres, and may accordingly exist both as enantiomers and as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present invention.

The preferred compounds of the formula (I), (Ia), (Ib), (Ic), (Id), (Ie), (If), (Ig) and (Ih) will have the 2- and 3- substituent cis and the preferred stereochemistry at the 2-position is that possessed by the compound of Example 1 (i.e. 2-(R)-), the preferred stereochemistry of the 3-position is that possessed by the compound of Example 1 (i.e. 3-(S)), and the preferred stereochemistry of the carbon to which the group Y is either (R) when Y is C_{1-4}alkyl (e.g. methyl) or (S) when Y is C_{1-4}alkyl substituted by hydroxy (e.g. CH_2OH). Thus for example as shown in formula (Ii)



(Ii)

The present invention further provides pharmaceutical compositions comprising one or more compounds of formula (I) in association with a pharmaceutically acceptable carrier.

Preferably the compositions according to the invention are in unit dosage forms such as tablets, pills, capsules, powders, granules, solutions or suspensions, or suppositories, for oral, parenteral or rectal administration, or administration by inhalation or insufflation.

For preparing solid compositions such as tablets, the principal active ingredient is mixed with a pharmaceutical carrier, e.g. conventional tableting ingredients such as corn starch, lactose, sucrose, sorbitol, talc, stearic acid, magnesium stearate, dicalcium phosphate or gums, and other pharmaceutical diluents, e.g. water, to form a solid preformulation composition containing a homogeneous mixture of a compound of the present invention, or a non-toxic pharmaceutically acceptable salt thereof. When referring to these preformulation compositions as homogeneous, it is meant that the active ingredient is dispersed evenly throughout the composition so that the composition may be readily subdivided into equally effective unit dosage forms such as tablets, pills and capsules. This solid preformulation composition is then subdivided into unit dosage forms of the type described above containing from 0.1 to about 500 mg of the active ingredient of the present invention. The tablets or pills of the novel composition can be coated or otherwise compounded to provide a dosage form affording the advantage of prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical

vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

Preferred compositions for administration by injection include those comprising a compound of formula (I), as the active ingredient, in association with a surface-active agent (or wetting agent or surfactant) or in the form of an emulsion (as a water-in-oil or oil-in-water emulsion).

Suitable surface-active agents include anionic agents such as sodium bis-(2-ethylhexyl)sulfosuccinate (docusate sodium), cationic agents, such as alkyltrimethylammonium bromides, (e.g. cetyltrimethylammonium bromide (cetrimide)), and in particular, non-ionic agents, such as polyoxyethylenesorbitans (e.g. Tween™ 20, 40, 60, 80 or 85) and other sorbitans (e.g. Span™ 20, 40, 60, 80 or 85). Compositions with a surface-active agent will conveniently comprise between 0.05 and 5% surface-active agent, and preferably between 0.1 and 2.5%. It will be appreciated that other ingredients may be added, for example mannitol or other pharmaceutically acceptable vehicles, if necessary.

Suitable emulsions may be prepared using commercially available fat emulsions, such as Intralipid™, Liposyn™, Infonutrol™, Lipofundin™ and Lipiphysan™. The active ingredient may be either dissolved in a pre-mixed emulsion composition or alternatively it may be dissolved in an oil (e.g. soybean oil, safflower oil, cottonseed oil, sesame oil, corn oil or almond oil) and an emulsion formed upon mixing with a phospholipid (e.g. egg phospholipids, soybean phospholipids or soybean lecithin) and water. It will be appreciated that other ingredients may be added, for example gylcerol or glucose, to adjust the tonicity of the emulsion. Suitable emulsions will typically contain up to 20% oil, for example, between 5 and 20%. The fat

emulsion will preferably comprise fat droplets between 0.1 and 1.0μm, particularly 0.1 and 0.5μm, and have a pH in the range of 5.5 to 8.0.

Particularly preferred emulsion compositions are those prepared by mixing a compound of formula (I) with Intralipid™ or the components thereof (soybean oil, egg phospholipids, glycerol and water).

Compositions for inhalation or insufflation include solutions and suspensions in pharmaceutically acceptable, aqueous or organic solvents, or mixtures thereof, and powders. The liquid or solid compositions may contain suitable pharmaceutically acceptable excipients as set out above. Preferably the compositions are administered by the oral or nasal respiratory route for local or systemic effect. Compositions in preferably sterile pharmaceutically acceptable solvents may be nebulised by use of inert gases. Nebulised solutions may be breathed directly from the nebulising device or the nebulising device may be attached to a face mask, tent or intermittent positive pressure breathing machine. Solution, suspension or powder compositions may be administered, preferably orally or nasally, from devices which deliver the formulation in an appropriate manner.

The present invention futher provides a process for the preparation of a pharmaceutical composition comprising a compound of formula (I), which process comprises bringing a compound of formula (I) into association with a pharmaceutically acceptable carrier or excipient.

The compounds of formula (I) are of value in the treatment of a wide variety of clinical conditions which are characterised by the presence of an excess of tachykinin, in particular substance P, activity. These may include disorders of the central nervous system such as anxiety, depression, psychosis and schizophrenia; epilepsy; neurodegenerative disorders such as dementia, including senile dementia of the Alzheimer type, Alzheimer's disease and Down's syndrome; demyelinating diseases such as MS and ALS and other neuropathological disorders such as peripheral neuropathy, for

example diabetic and chemotherapy-induced neuropathy, and postherpetic and other neuralgias; small cell carcinomas such as small cell lung cancer; respiratory diseases, particularly those associated with excess mucus secretion such as chronic obstructive airways disease, bronchopneumonia, chronic bronchitis, cystic fibrosis and asthma, and bronchospasm; inflammatory diseases such as inflammatory bowel disease, psoriasis, fibrositis, osteoarthritis, rheumatoid arthritis, pruritis and sunburn; allergies such as eczema and rhinitis; hypersensitivity disorders such as poison ivy; ophthalmic diseases such as conjunctivitis, vernal conjunctivitis, and the like; ophthalmic conditions associated with cell proliferation such as proliferative vitreoretinopathy; cutaneous diseases such as contact dermatitis, atopic dermatitis, urticaria, and other eczematoid dermatitis; addiction disorders such as alcoholism; stress related somatic disorders; reflex sympathetic dystrophy such as shoulder/hand syndrome; dysthymic disorders; adverse immunological reactions such as rejection of transplanted tissues and disorders related to immune enhancement or suppression such as systemic lupus erythematosus; gastrointestinal (GI) disorders and diseases of the GI tract such as disorders associated with the neuronal control of viscera, ulcerative colitis, Crohn's disease, irritable bowel syndrome and emesis, including acute, delayed or anticipatory emesis such as emesis induced by chemotherapy, radiation, toxins, viral or bacterial infections, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure, in particular, for example, drug or radiation induced emesis or post-operative nausea and vomiting; disorders of bladder function such as cystitis, bladder detrusor hyper-reflexia and incontinence; fibrosing and collagen diseases such as scleroderma and eosinophilic fascioliasis; disorders of blood flow caused by vasodilation and vasospastic diseases such as angina, migraine and Reynaud's disease; and pain or nociception, for example, that

attributable to or associated with any of the foregoing conditions, especially the transmission of pain in migraine.

The compounds of formula (I) are also of value in the treatment of a combination of the above conditions, in particular in the treatment of combined post-operative pain and post-operative nausea and vomiting.

The compounds of formula (I) are particularly useful in the treatment of emesis, including acute, delayed or anticipatory emesis, such as emesis induced by chemotherapy, radiation, toxins, pregnancy, vestibular disorders, motion, surgery, migraine, and variations in intercranial pressure. Most especially, the compounds of formula (I) are of use in the treatment of emesis induced by antineoplastic (cytotoxic) agents including those routinely used in cancer chemotherapy.

Examples of such chemotherapeutic agents include alkylating agents, for example, nitrogen mustards, ethyleneimine compounds, alkyl sulphonates and other compounds with an alkylating action such as nitrosoureas, cisplatin and dacarbazine; antimetabolites, for example, folic acid, purine or pyrimidine antagonists; mitotic inhibitors, for example, vinca alkaloids and derivatives of podophyllotoxin; and cytotoxic antibiotics.

Particular examples of chemotherapeutic agents are described, for instance, by D. J. Stewart in *Nausea and Vomiting: Recent Research and Clinical Advances*, Eds. J. Kucharczyk *et al*, CRC Press Inc., Boca Raton, Florida, USA (1991) pages 177-203, especially page 188. Commonly used chemotherapeutic agents include cisplatin, dacarbazine (DTIC), dactinomycin, mechlorethamine (nitrogen mustard), streptozocin, cyclophosphamide, carmustine (BCNU), lomustine (CCNU), doxorubicin (adriamycin), daunorubicin, procarbazine, mitomycin, cytarabine, etoposide, methotrexate, 5-fluorouracil, vinblastine, vincristine, bleomycin and chlorambucil [R. J. Gralla *et al* in *Cancer Treatment Reports* (1984) 68(1), 163-172].

The compounds of formula (I) are also of use in the treatment of emesis induced by radiation including radiation therapy such as in the treatment of cancer, or radiation sickness; and in the treatment of post-operative nausea and vomiting.

It will be appreciated that the compounds of formula (I) may be presented together with another therapeutic agent as a combined preparation for simultaneous, separate or sequential use for the relief of emesis. Such combined preparations may be, for example, in the form of a twin pack.

A further aspect of the present invention comprises the compounds of formula (I) in combination with a 5-HT_3 antagonist, such as ondansetron, granisetron or tropisetron, or other anti-emetic medicaments, for example, a dopamine antagonist such as metoclopramide. Additionally, a compound of formula (I) may be administered in combination with an anti-inflammatory corticosteroid, such as dexamethasone. Furthermore, a compound of formula (I) may be administered in combination with a chemotherapeutic agent such as an alkylating agent, antimetabolite, mitotic inhibitor or cytotoxic antibiotic, as described above. In general, the currently available dosage forms of the known therapeutic agents for use in such combinations will be suitable.

When tested in the ferret model of cisplatin-induced emesis described by F. D. Tattersall *et al*, in *Eur. J. Pharmacol.*, (1993) 250, R5-R6, the compounds of the present invention were found to attenuate the retching and vomiting induced by cisplatin.

The compounds of formula (I) are also particularly useful in the treatment of pain or nociception and/or inflammation and disorders associated therewith such as, for example, neuropathy, such as diabetic and chemotherapy-induced neuropathy, postherpetic and other neuralgias, asthma, osteroarthritis, rheumatoid arthritis and especially migraine.

The present invention further provides a compound of formula (I) for use in therapy.

According to a further or alternative aspect, the present invention provides a compound of formula (I) for use in the manufacture of a medicament for the treatment of physiological disorders associated with an excess of tachykinins, especially substance P.

The present invention also provides a method for the the treatment or prevention of physiological disorders associated with an excess of tachykinins, especially substance P, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound of formula (I) or a composition comprising a compound of formula (I).

For the treatment of certain conditions it may be desirable to employ a compound according to the present invention in conjunction with another pharmacologically active agent. For example, for the treatment of respiratory diseases such as asthma, a compound of formula (I) may be used in conjunction with a bronchodilator, such as a β_2-adrenergic receptor antagonist or tachykinin antagonist which acts at NK-2 receptors. The compound of formula (I) and the bronchodilator may be administered to a patient simultaneously, sequentially or in combination.

The present invention accordingly provides a method for the treatment of a respiratory disease, such as asthma, which method comprises administration to a patient in need thereof of an effective amount of a compound of formula (I) and an effective amount of a bronchodilator.

The present invention also provides a composition comprising a compound of formula (I), a bronchodilator, and a pharmaceutically acceptable carrier.

The excellent pharmacological profile of the compounds of the present invention offers the opportunity for their use in therapy at low doses thereby minimising the risk of unwanted side effects.

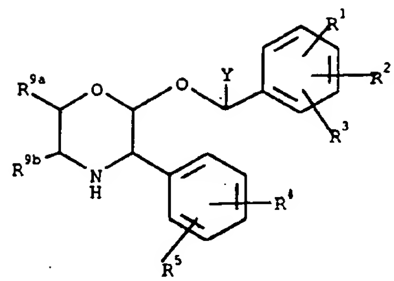
In the treatment of the conditions associated with an excess of tachykinins, a suitable dosage level is about 0.001 to 50 mg/kg per day, in particular about 0.01 to about 25 mg/kg, such as from about 0.05 to about 10 mg/kg per day.

For example, in the treatment of conditions involving the neurotransmission of pain sensations, a suitable dosage level is about 0.001 to 25 mg/kg per day, preferably about 0.005 to 10 mg/kg per day, and especially about 0.005 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

In the treatment of emesis using an injectable formulation, a suitable dosage level is about 0.001 to 10 mg/kg per day, preferably about 0.005 to 5 mg/kg per day, and especially 0.01 to 2 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day, preferably once or twice per day.

It will be appreciated that the amount of a compound of formula (I) required for use in any treatment will vary not only with the particular compounds or composition selected but also with the route of administration, the nature of the condition being treated, and the age and condition of the patient, and will ultimately be at the discretion of the attendant physician.

According to a general process (A), the compounds according to the invention may be prepared from compounds of formula (II)



(II)

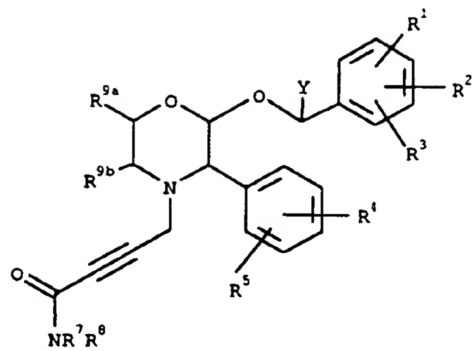
wherein R^1, R^2, R^3, R^4, R^5 and Y are as defined in relation to formula (I) by reaction with a compound of formula (III):

$$X^1\text{-}X\text{-}R^{6a} \qquad \text{(III)}$$

where X is as defined in relation to formula (I), R^{6a} is a group of the formula R^6 as defined in relation to formula (Ia) or a precursor therefor and X^1 is a leaving group such as bromine or chlorine; and, if R^{6a} is a precursor group, converting it to a group R^6 (in which process any reactive group may be protected and thereafter deprotected if desired).

This reaction may be performed in conventional manner, for example in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

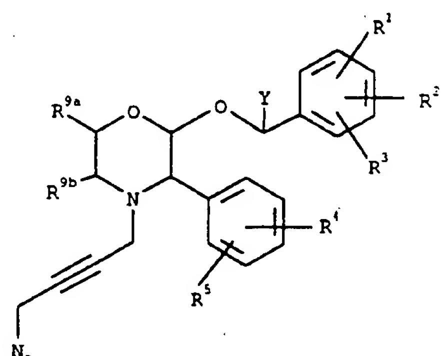
According to another process (B), compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$, may be prepared by reaction of a compound of formula (IV)



(IV)

with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at a temperature of between 40°C and 100°C, followed by reduction of the carbonyl group adjacent to $-NR^7R^8$ using a suitable reducing agent such as lithium aluminium hydride at at a temperature between -10°C and room temperature, conveniently at room temperature.

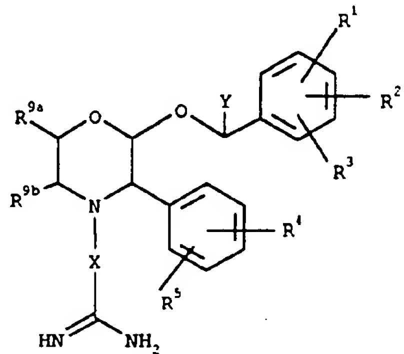
Alternatively, according to a process (C), compounds of formula (I) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$, and X is $-CH_2-$, may be prepared by reaction of a compound of formula (V)



(V)

with an amine of formula NHR^7R^8, in a suitable solvent such as an ether, for example, dioxan, at elevated temperature, for example, between 50°C and 100°C, in a sealed tube, or the like. This reaction is based upon that described in *Chemische Berichte* (1989) 122, p. 1963.

According to another process, (D), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine may be prepared by reaction of intermediates of formula (VI):

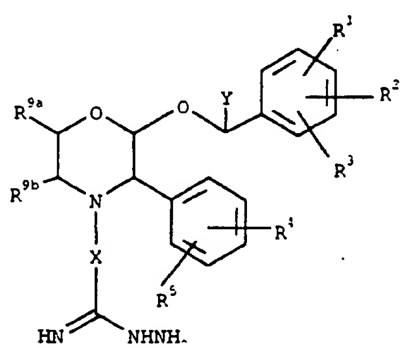


(VI)

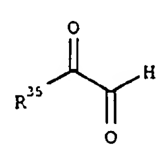
with substituted or unsubstituted 1,3,5-triazine.

The reaction is conveniently effected in a suitable organic solvent, such as acetonitrile, at elevated temperature, such as 80-90°C, preferably about 82°C.

According to a further process, (E), compounds of formula (I) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine may be prepared by reaction of an intermediate of formula (VII) with a dicarbonyl compound of formula (VIII):



(VII)

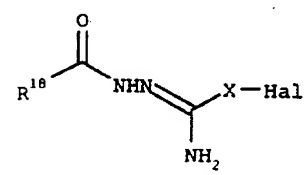


(VIII)

wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8.

The reaction is conveniently effected in a suitable organic solvent, such as an ether, e.g. tetrahydrofuran, conveniently at ambient temperature.

According to a further process (F), compounds of formula (I) wherein R^6 represents a substituted 1,2,4-triazolyl group may be prepared by reaction of an intermediate of formula (II) with a compound of formula (IX)



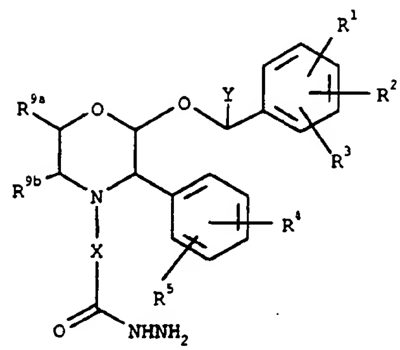
(IX)

wherein X is as defined in relation to formula (I), Hal is a halogen atom, for example, bromine, chlorine or iodine and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I), for example, by reduction of the $CONH_2$ group to CH_2NH_2.

Suitable bases of use in the reaction include alkali metal carbonates such as, for example, potassium carbonate. The reaction is conveniently effected in an anhydrous organic solvent such as, for example, anhydrous dimethylformamide, preferably at elevated temperature, such as about 140°C.

A suitable reducing agent for the group $CONH_2$ is lithium aluminium hydride, used at between -10°C and room temperature.

According to another process, (G), compounds of formula (I) wherein R^6 represents thioxotriazolyl may be prepared from intermediates of formula (X)



(X)

by reaction with a compound of formula HNCS, in the presence of a base.

Suitable bases of use in the reaction include organic bases such as, for example, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). The reaction is conveniently effected in a suitable organic solvent, such as alcohol, e.g. butanol.

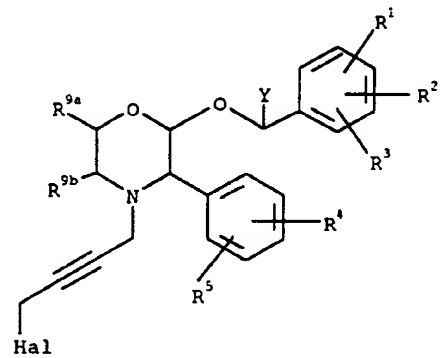
Further details of suitable procedures will be found in the accompanying Examples.

Compounds of formula (I) may also be prepared from other compounds of formula (I) using suitable interconversion procedures. For example, compounds of formula (I) wherein X represents C_{1-4}alkyl may be prepared from compounds of formula (I) wherein X represents C_{1-4}alkyl substituted by oxo by reduction, for example, using borane or lithium aluminium hydride. Suitable interconversion procedures will be readily apparent to those skilled in the art.

Intermediates of formula (IV) may be prepared from intermediates of formula (II) by reaction with an acetylene compound of formula $HC{\equiv}C\text{-}CH_2\text{-}Hal$ in the presence of a base such as potassium carbonate in a suitable solvent such as dimethylformamide, conveniently at room temperature, followed by reaction of the resultant acetylene intermediate with an amide of formula Hal-CO-NR^7R^8 in the presence of suitable catalysts including bis(triphenylphosphine) palladium(II) chloride,

copper(I) iodide and triphenylphosphine in a suitable solvent such as triethylamine, preferably at reflux.

Intermediates of formula (V) may be prepared from a compound of formula (XI)



(XI)

wherein Hal is a halogen atom, for example, chlorine, bromine or iodine, especially chlorine, by reaction with an azide, for example, sodium azide in a suitable solvent such as dimethylsulphoxide at or below room temperature.

Compounds of formula (XI) may be prepared by a dropwise addition of an intermediate of formula (II) to a dihaloacetylene of formula Hal-CH_2-C≡C-CH_2-Hal where each Hal is independently chlorine, bromine or iodine, especially chlorine. The reaction is conveniently effected in a suitable solvent such as dimethylformamide in the presence of a base such as potassium carbonate.

Intermediates of formula (VI) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-X-C(NH)NH_2, where Hal and X are as previously defined.

Intermediates of formula (VII) may be prepared from intermediates of formula (II) by reaction with a compound of formula Hal-X-C(NH)NHNH-Boc, wherein Hal and X are as previously defined and Boc stands for t-butoxycarbonyl, followed by deprotection under acidic conditions.

Compounds of formula (VIII) are commercially available or may be prepared from commercially available compounds by known methods.

Compounds of formula (IX) may be prepared as described in *J. Med. Chem.*, (1984) 27, 849.

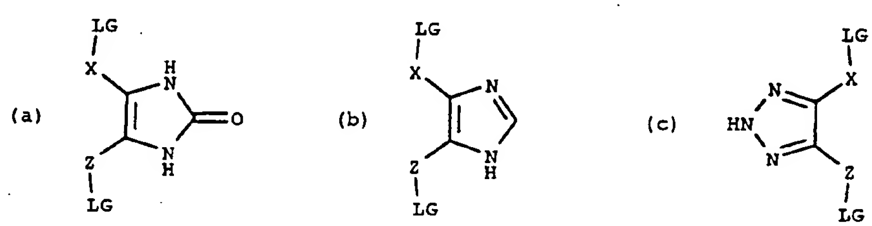
Intermediates of formula (X) may be prepared from the corresponding ester by treatment with hydrazine. The reaction is conveniently effected in a suitable organic solvent, such as an alcohol, for example, ethanol, at elevated temerpature.

For compounds wherein R^6 is a heterocycle substituted by a ZNR^7R^8 group where Z is CH_2, certain favoured compounds of formula (I) may be prepared from a corresponding compound with a hydrogen atom in place of the ZNR^7R^8. Thus, for example a compound of the formula (I) wherein R^6 is an imidazolinone group carrying a $CH_2NR^7R^8$ moiety may be prepared from a corresponding compound lacking the $CH_2NR^7R^8$ moiety by reaction with formaldehyde and an amine NHR^7R^8 under conventional Mannich reaction conditions, for example in methanol with heating. If desired a pre-formed reagent such as $R^7R^8N^+{=}CH_2.I^-$ may be employed and a tertiary amine such as triethylamine used as acid acceptor.

Alternatively a compound of formula (I) wherein R^6 is an imidazolinone group lacking a $CH_2NR^7R^8$ may be reacted with paraformaldehyde and an amine for example a secondary amine such as pyrrolidine to give a compound wherein the imidazolinone ring is substituted by $CH_2NR^7R^8$ where R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom or a second nitrogen atom which will be part of a NH or NR^c moiety, where R^c is as previously defined.

This reaction may be performed in a conventional manner, for instance, in a suitable solvent such as an alcohol, for example, methanol at an elevated temperature up to the boiling point of the solvent.

A further alternative method for the preparation of certain compounds of formula (I) involves the reaction of an intermediate of formula (II) as defined above with one of the compounds of formula (XII):



(XII)

wherein each LG, which may be the same or different, is a leaving group, such as an alkyl- or arylsulphonyloxy group (e.g. mesylate or tosylate) or, in particular, a halogen atom, (e.g. bromine, chlorine or iodine) and X and Z are as defined in formula (I), followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety.

This reaction is conveniently effected in an organic solvent such as dimethylformamide in the presence of an acid acceptor such as potassium carbonate.

It will be appreciated that, where necessary, reactive groups may be protected, thus for example, the NH groups of an imidazolinone of formula (XIIa) may be protected by any suitable amine protecting group such as an acetyl group.

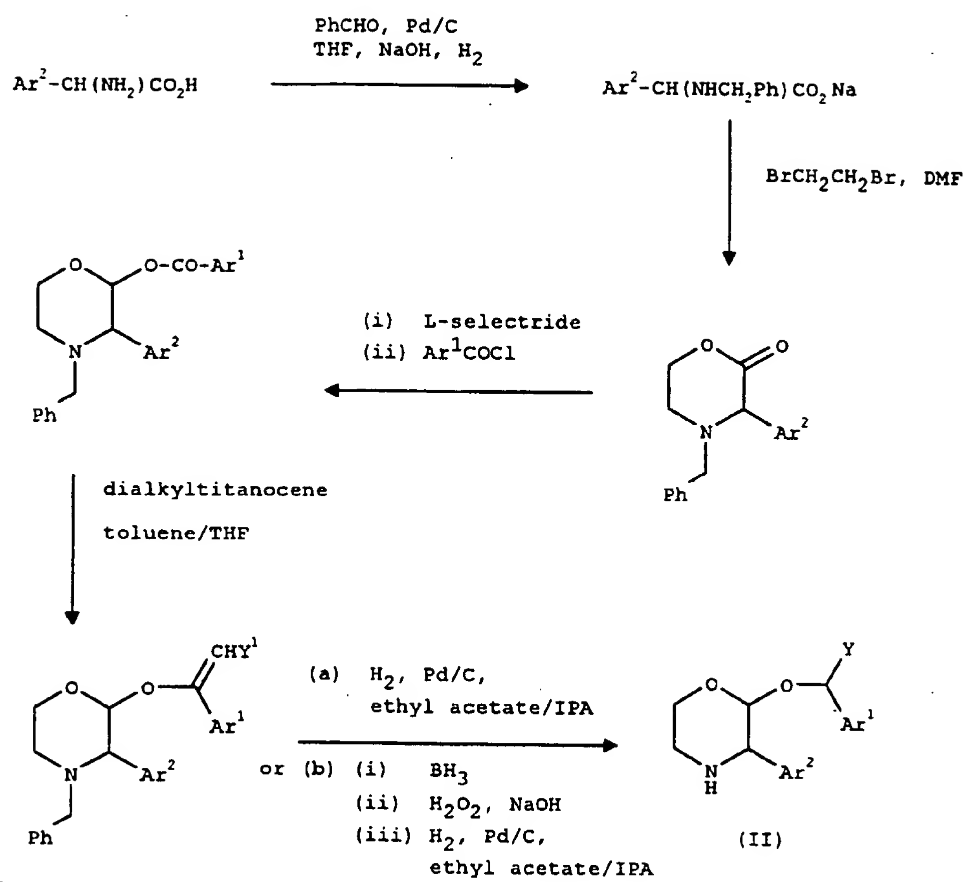
The preferred phosphate prodrugs of the compounds of the present invention may be prepared in a stepwise manner from a compound of formula (I) wherein Y is, for example, $-CH_2OH-$.

Thus, the hydroxy compound is first treated with dibenzyloxydiethylaminophosphine in a suitable solvent such as tetrahydrofuran, preferably in the presence of an acid catalyst such as tetrazole. The resultant compound ($Y = CH_2OP(OCH_2Ph)_2$) is then oxidised

using, for example, 4-methylmorpholine-N-oxide to give the dibenzyl-protected phosphate. Deprotection by catalytic hydrogenation or transfer hydrogenation (palladium catalyst on carbon and ammonium formate), in a suitable solvent such as methanol at reflux, yields the desired phosphate prodrug which may be converted to any desired salt form by conventional methodology.

In an alternative two-step method, the hydroxy compound of formula (I) may be reacted with a suitable base such as sodium hydride in tetrahydrofuran, and tetrabenzylpyrophosphate added to yield the dibenzyl-protected phosphate which may be deprotected as described above.

The compounds of the formula (II) may be prepared as shown in the following Scheme in which Ar^1 represents the R^1, R^2, R^3 substituted phenyl group; Ar^2 represents the R^4, R^5 substituted phenyl group and Ph represents phenyl:



(Y^1 = H or C_{1-3}alkyl)

L-Selectride is lithium tri-sec-butylborohydride.

The following references describe methods which may be applied by the skilled worker to the chemical synthesis set forth above once the skilled worker has read the disclosure herein:

(i) D.A. Evans *et al., J. Am. Chem. Soc.*, (1990) 112, 4011.
(ii) I. Yanagisawa *et al., J. Med. Chem.*, (1984) 27, 849.
(iii) R. Duschinsky *et al., J. Am. Chem. Soc.*, (1948) 70, 657.
(iv) F.N. Tebbe *et al., J. Am. Chem. Soc.*, (1978) 100, 3611.
(v) N.A. Petasis *et al., J. Am. Chem. Soc.*, (1990) 112, 6532.
(vi) K. Takai *et al., J. Org. Chem.*, (1987) 52, 4412.

The Examples disclosed herein produce predominently the preferred isomers. The unfavoured isomers are also produced as minor components. If desired they may be isolated and employed to prepare the various stereoisomers in conventional manner, for example chromatography using an appropriate column. However, the skilled worker will appreciate that although the Examples have been optimized to the production of the preferred isomers, variation in solvent, reagents, chromatography etc can be readily employed to yield the other isomers.

It will be appreciated that compounds of the formula (I) wherein R^6 contains an =O or =S substituent can exist in tautomeric forms. All such tautomeric forms and mixtures thereof are included within this invention. Most aptly the =O or =S substituent in R^6 is the =O substituent.

Where they are not commercially available, the intermediates of formula (III) above may be prepared by the procedures described in the accompanying Examples or by alternative procedures which will be readily apparent to one skilled in the art.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting groups, such as those described in *Protective Groups in Organic Chemistry*, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene and P.G.M. Wuts, *Protective Groups in Organic Synthesis*, John Wiley & Sons, 1991. The protecting groups may be removed at a convenient subsequent stage using methods known from the art.

The exemplified compounds of this invention were tested by the methods set out at pages 36 to 39 of International Patent Specification No. WO 93/01165. The compounds or, in the case of prodrugs, the parent compounds, were found to be active with IC_{50} at the NK_1 receptor of less than 10nM on said test method.

DESCRIPTION 1

(S)-(4-Fluorophenyl)glycine

Via Chiral Synthesis:

Step A: 3-(4-Fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1 L 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.09g (33.0mmol) of 4-fluorophenylacetic acid in 100ml of anhydrous ether. The solution was cooled to -10°C and treated with 5.60ml (40.0mmol) of triethylamine followed by 4.30ml (35.0mmol) of trimethylacetyl chloride. A white precipitate formed immediately. The resulting mixture was stirred at -10°C for 40 minutes, then cooled to -78°C.

An oven-dried, 250ml round bottom flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 5.31g (30.0mmol) of 4-(S)-benzyl-2-oxazolidinone in 40ml of dry THF. The solution was stirred in a dry ice/acetone bath for 10 minutes, then 18.8ml of 1.6M n-butyllithium solution in hexanes was slowly added. After 10 minutes, the lithiated oxazolidinone solution was added, via cannula, to the above mixture in the 3-necked flask. The cooling bath was removed from the resulting mixture and the temperature was allowed to rise to 0°C. The reaction was quenched with 100ml of saturated aqueous ammonium chloride solution, transferred to a 1l flask, and the ether and THF were removed *in vacuo*. The concentrated mixture was partitioned between 300ml of methylene chloride and 50ml of water and the layers were separated. The organic layer was washed with 100ml of 2N aqueous hydrochloric acid solution, 300ml of saturated aqueous sodium bicarbonate

solution, dried over magnesium sulfate and concentrated *in vacuo*. Flash chromatography on 400g of silica gel using 3:2 v/v hexanes/ether as the eluant afforded 8.95g of an oil that slowly solidified on standing. Recrystallisation from 10:1 hexanes/ether afforded 7.89g (83%) of the title compound as a white solid: mp 64-66°C. MS (FAB): m/z 314 (M^++H, 100%), 177 (M-ArCH_2CO+H, 85%). ^{1}H NMR (400MHz, $CDCl_3$) δ 2.76 (1H, dd, J=13.2, 9.2), 3.26 (dd, J=13.2, 3.2), 4.16-4.34 (4H, m), 4.65 (1H, m), 7.02-7.33 (9H, m). Anal. Calcd for $C_{18}H1_6FNO_3$; C, 69.00; H, 5.15; N, 4.47; F, 6.06; Found: C, 68.86; H, 5.14; N, 4.48; F, 6.08.

Step B: 3-((S)-Azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone

An oven-dried, 1l 3-necked flask, equipped with a septum, nitrogen inlet, thermometer, and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 58.0ml of 1M potassium bis(trimethylsilyl)amide solution in toluene and 85ml of THF and was cooled to -78°C. An oven-dried 250ml round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 7.20g (23.0mmol) of 3-(4-fluorophenyl)acetyl-4-(S)-benzyl-2-oxazolidinone (from Step A) in 40ml of THF. The acyl oxazolidinone solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the potassium bis(trimethylsilyl)amide solution at such a rate that the internal temperature of the mixture was maintained below -70°C. The acyl oxazolidinone flask was rinsed with 15ml of THF and the rinse was added, via cannula, to the reaction mixture and the resulting mixture was stirred at -78°C for 30 minutes. An oven-dried, 250ml

round-bottomed flask, equipped with a septum and a magnetic stirring bar, was flushed with nitrogen and charged with a solution of 10.89g (35.0mmol) of 2,4,6-triisopropylphenylsulfonyl azide in 40ml of THF. The azide solution was stirred in a dry ice/acetone bath for 10 minutes, then transferred, via cannula, to the reaction mixture at such a rate that the internal temperature of the mixture was maintained below -70°C. After 2 minutes, the reaction was quenched with 6.0ml of glacial acetic acid, the cooling bath was removed and the mixture was stirred at room temperature for 18 hours. The quenched reaction mixture was partitioned between 300ml of ethyl acetate and 300ml of 50% saturated aqueous sodium bicarbonate solution. The organic layer was separated, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 500g of silica gel using 2:1 v/v, then 1:1 v/v hexanes/methylene chloride as the eluant afforded 5.45g (67%) of the title compound as an oil. IR Spectrum (neat, cm^{-1}): 2104, 1781, 1702. ^1H NMR (400MHz, $CDCl_3$) δ 2.86 (1H, dd, J=13.2, 9.6), 3.40 (1H, dd, J=13.2, 3.2), 4.09-4.19 (2H, m), 4.62-4.68 (1H, m), 6.14 (1H, s), 7.07-7.47 (9H, m). Anal. Calcd. for $C_{18}H_{15}FN_4O_3$; C 61.01; H, 4.27; N, 15.81; F, 5.36; Found: C, 60.99; H, 4.19; N, 15.80; F, 5.34.

Step C: (S)-Azido-(4-fluorophenyl)acetic acid

A solution of 5.40g (15.2mmol) of 3-((S)-azido-(4-fluorophenyl))acetyl-4-(S)-benzyl-2-oxazolidinone (from Step B) in 200ml of 3:1 v/v THF/water was stirred in an ice bath for 10 minutes. 1.28g (30.4mmol) of lithium hydroxide monohydrate was added in one portion and the resulting mixture was stirred cold for 30 minutes. The reaction mixture was partitioned between 100ml of

methylene chloride and 100ml of 25% saturated aqueous sodium bicarbonate solution and the layers were separated. The aqueous layer was washed with 2 x 100ml of methylene chloride and acidified to pH 2 with 2N aqueous hydrochloric acid solution. The resulting mixture was extracted with 2 x 100ml of ethyl acetate; the extracts were combined, washed with 50ml of saturated aqueous sodium chloride solution, dried over magnesium sulfate, and concentrated *in vacuo* to afford 2.30g (77%) of the title compound as an oil that was used in the following step without further purification. IR Spectrum (neat, cm^{-1}): 2111, 1724. ^1H NMR (400MHz, $CDCl_3$) δ 5.06 (1H, s), 7.08-7.45 (4H, m), 8.75 (1H, br s).

Step D: (S)-(4-Fluorophenyl)glycine

A mixture of 2.30g (11.8mmol) of (S)-azido-(4-fluorophenyl)acetic acid (from Step C), 250mg 10% palladium on carbon catalyst and 160ml 3:1 v/v water/acetic acid was stirred under an atmosphere of hydrogen for 18 hours. The reaction mixture was filtered through Celite and the flask and filter cake were rinsed well with ~1l of 3:1 v/v water/acetic acid. The filtrate was concentrated *in vacuo* to about 50ml of volume. 300ml of toluene was added and the mixture concentrated to afford a solid. The solid was suspended in 1:1 v/v methanol/ether, filtered and dried to afford 1.99g (100%) of the title compound. ^1H NMR (400MHz, D_2O+ NaOD) δ 3.97 (1H, s), 6.77 (2H, app t, J=8.8), 7.01 (2H, app t, J=5.6).

Via Resolution:

Step A' (4-Fluorophenyl)acetyl chloride

A solution of 150g (0.974mol) of 4-(fluorophenyl)acetic acid and 1ml of N,N-dimethylformamide in 500ml of toluene at 40°C was treated with 20ml of thionyl chloride and heated to 40°C. An additional 61.2ml of thionyl chloride was added dropwise over 1.5 hours. After the addition, the solution was heated at 50°C for 1 hour, the solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 150.4g (89.5%) of the title compound, bp=68-70°C.

Step B': Methyl 2-bromo-3-(4-fluorophenyl)acetate

A mixture of 150.4g (0.872mol) of 4-(fluorophenyl)acetyl chloride (from Step A') and 174.5g (1.09mol) of bromine was irradiated at 40-50°C with a quartz lamp for 5 hours. The reaction mixture was added dropwise to 400ml of methanol and the solution was stirred for 16 hours. The solvent was removed *in vacuo* and the residual oil was distilled at reduced pressure (1.5mmHg) to afford 198.5g (92%) of the title compound, bp=106-110°C.

Step C': Methyl (±)-(4-fluorophenyl)glycine

A solution of 24.7g (0.1mol) of methyl 2-bromo-2-(4-fluorophenyl)acetate (from Step B') and 2.28g (0.01mol) of benzyl triethylammonium chloride in 25ml of methanol was treated with 6.8g (0.105mol) of sodium azide and the resulting mixture was stirred for 20 hours at room temperature. The reaction mixture was filtered; the filtrate was diluted with 50ml of methanol and hydrogenated in the presence of 0.5g of 10% Pd/C at 50 psi for 1 hour. The solution was filtered and the solvent removed *in vacuo*. The residue was partitioned between 10% aqueous sodium carbonate solution and ethyl acetate. The organic phase was

washed with water, saturated aqueous sodium chloride solution dried over magnesium sulfate and concentrated *in vacuo* to afford 9.8g of the title compound as an oil.

Step D': Methyl (S)-(4-fluorophenyl)glycinate

A solution of 58.4g of methyl (±) 4-(fluorophenyl)glycinate (from Step C') in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(+)-dibenzoyltartaric acid ((+)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crystallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 32.4g of methyl (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee=93.2%). The mother liquors were concentrated *in vacuo* and the free base was liberated by partitioning between ethyl acetate and aqueous sodium carbonate solution. A solution of free base, so obtained, in 110ml of 7:1 v/v ethanol/water was mixed with a solution of 28.6g (0.0799mol) of O,O'-(-)-dibenzoyltartaric acid ((-)-DBT) (28.6g, 0.0799mol) in 110ml of 7:1 v/v ethanol:water and the resulting solution was allowed to age at room temperature. Ethyl acetate (220ml) was added after crysallisation was complete and the resulting mixture was cooled to -20°C and filtered to afford 47.0g of methyl (R)-(4-fluorophenyl)glycinate, (-)-DBT salt (ee=75.8%). Recycling of the mother liquors and addition of (+)-DBT gave a second crop of 7.4g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt (ee=96.4%). The two crops of the (S)-amino ester (39.8g) were combined in 200ml of 7:1 v/v ethanol/water, heated for 30 minutes and cooled to room temperature. Addition of ethyl acetate, cooling, and filtration afforded 31.7g of (S)-(4-

fluorophenyl)glycinate, (+)-DBT salt (ee > 98%). Enantiomeric excess was determined by chiral HPLC (Crownpak CR(+) 5% MeOH in aq $HClO_4$ pH2 1.5ml/min 40°C 200nm).

A mixture of 17.5g of (S)-(4-fluorophenyl)glycinate, (+)-DBT salt and 32ml of 5.5N HCl (32ml) was heated at reflux for 1.5 hours. The reaction mixture was concentrated *in vacuo* and the residue was dissolved in 40ml of water. The aqueous solution was washed (3 x 30ml of ethyl acetate) and the layers were separated. The pH of the aqueous layer was adjusted to 7 using ammonium hydroxide and the precipitated solid was filtered to afford 7.4g of the title compound (ee=98.8%).

DESCRIPTION 2

4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

Step A: N-Benzyl-(S)-(4-fluorophenyl)glycine

A solution of 1.87g (11.05mmol) of (S)-(4-fluorophenyl)-glycine (from Description 1) and 1.12ml (11.1mmol) of benzaldehyde in 11.1ml of 1N aqueous sodium hydroxide solution and 11ml of methanol at 0°C was treated with 165mg (4.4mmol) of sodium borohydride. The cooling bath was removed and the resulting mixture was stirred at room temperature for 30 minutes. Second portions of benzaldehyde (1.12ml (11.1mmol)) and sodium borohydride (165mg (4.4mmol) were added to the reaction mixture and stirring was continued for 1.5hours. The reaction mixture was partitioned between 100ml of ether and 50ml of water and the layers were separated. The aqueous layer was separated and filtered to remove a small amount of insoluble material. The filtrate was acidified to pH 5 with 2N aqueous hydrochloric acid solution

and the solid that had precipitated was filtered, rinsed well with water, then ether, and dried to afford 1.95g of the title compound. ^{1}H NMR (400MHz, D_2O + NaOD) δ 3.33 (2H, AB q, J=8.4), 3.85 (1H, s), 6.79-7.16 (4H, m).

Step B: 4-Benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone

A mixture of 1.95g (7.5mmol) of N-benzyl (S)-(4-fluorophenyl)glycine, 3.90ml (22.5mmol) of N,N-diisopropyl-ethylamine, 6.50ml (75.0mmol) of 1,2-dibromoethane and 40ml of N,N-dimethylformamide was stirred at 100°C for 20 hours (dissolution of all solids occurred on warming). The reaction mixture was cooled and concentrated *in vacuo*. The residue was partitioned between 250ml of ether and 100ml of 0.5N potassium hydrogen sulfate solution and the layers were separated. The organic layer was washed with 100ml of saturated aqueous sodium bicarbonate solution, 3 x 150ml of water, dried over magnesium sulfate, and concentrated *in vacuo*. Flash chromatography on 125g of silica gel using 3:1 v/v hexanes/ether as the eluant afforded 1.58g (74%) of the title compound as an oil. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.65 (1H, dt, J=3.2, 12.8), 3.00 (1H, dt, J=12.8, 2.8), 3.16 (1H, d, J=13.6), 3.76 (1H, d, J=13.6), 4.24 (1H, s), 4.37 (1H, dt, J=13.2, 3.2), 4.54 (1H, dt, J=2.8, 13.2), 7.07-7.56 (9H, m).

DESCRIPTION 3

4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of 2.67g (10.0mmol) of 4-benzyl-3-(S)-(4-fluorophenyl)-2-morpholinone (Description 2) in 40ml of dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of

1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml(20.0mmol) of 3,5-bis(trifluoromethyl)benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. ^{1}H NMR (200MHz, $CDCl_3$) δ 2.50 (1H, dt, J=3.4, 12.0), 2.97 (1H, app d, J=12.0), 2.99 (1H, d, J=13.6), 3.72-3.79 (1H, m), 3.82 (1H, d, J=2.6), 4.00 (1H, d, J=13.6), 4.20 (dt, J=2.4, 11.6), 6.22 (1H, d, J=2.6), 7.22-7.37 (7H, m), 7.57 (2H, app d, J=6.8), 8.07 (1H, s), 8.47 (2H, s). MS (FAB) m/z 528 (M+H, 25%), 270 (100%). Anal. Calcd for $C_{26}H_{20}F_7NO_3$: C, 59.21; H, 3.82; N, 2.66; F, 25.21. Found: C, 59.06; H, 4.05; N, 2.50; F, 25.18.

DESCRIPTION 4

4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

Step A: Dimethyl titanocene

A solution of 2.49g (10.0mmol) of titanocene dichloride in 50ml of ether in the dark at 0°C was treated with 17.5ml of 1.4M

methyllithium solution in ether maintaining the internal temperature below 5°C. The resulting yellow/orange mixture was stirred at room temperature for 30 minutes and the reaction was quenched by slowly adding 25g of ice. The quenched reaction mixture was diluted with 50ml of ether and 25ml of water and the layers were separated. The organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 2.03g (98%) of the title compound as a light-sensitive solid. The dimethyl titanocene could be stored as a solution in toluene at 0°C for at least 2 weeks without apparent chemical degradation. ^{1}H NMR (200MHz, $CDCl_3$) δ -0.15 (6H, s), 6.06 (10H, s).

Step B: 4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-(4-fluorophenyl)morpholine

A solution of the compound of Description 3 (2.50g, 4.9mmol) and 2.50g (12.0mmol) of dimethyl titanocene (from Step A) in 35ml of 1:1 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. An analytical sample was obtained via recrystallisation from isopropanol: ^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (1H, dt, J=3.6, 12.0), 2.90 (1H, app d, J=12.0), 2.91 (1H, d, J=13.6), 3.62-3.66 (1H, m), 3.72 (1H, d, J=2.6), 3.94 (1H, d, J=13.6), 4.09 (1H, dt, J=2.4, 12.0), 4.75 (1H, d, J=3.2), 4.82 (1H, d, J=3.2), 5.32 (1H, d, J=2.6), 7.09 (2H, t, J=8.8), 7.24-7.33 (5H, m), 7.58-7.62 (2H, m), 7.80 (1H, s), 7.90 (2H, s); MS (FAB) 526 (M+H, 75%), 270 (100%). Anal. Calcd for $C_{27}H_{22}F_7NO_2$: C, 61.72; H, 4.22; N, 2.67; F, 25.31. Found: C, 61.79; H, 4.10; N, 2.65; F, 25.27%.

DESCRIPTION 5

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 4 (4.0g) was dissolved in ethyl acetate (50ml) and isopropanol (16ml). To this solution was added palladium on charcoal (1.5g) and the mixture was hydrogenated at 40 psi for 36h. The catalyst was removed by filtration through Celite and the solvents were removed *in vacuo*. The residue was purified by flash chromatography on silica using 100% ethyl acetate and then 1-10% methanol in ethyl acetate. This afforded isomer A 500mg (15%) and isomer B 2.6g (80%) as clear oils - isomer B crystallised on standing. For the title compound: ^1H NMR (400MHz, $CDCl_3$) δ 1.16 (3H, d, J=6.8MHz), 1.80 (1H, br s), 3.13 (1H, dd, J=3.2, 12.4Hz), 3.23 (1H, dt, J=3.6, 12.4Hz), 3.63 (1H, dd, J=2.4, 11.2Hz), 4.01 (1H, d, J=2.4Hz), 4.13 (1H, dt, J=3.2, 12.0Hz), 4.42 (1H, d, J=2.4Hz), 4.19 (1H, q, J=6.8Hz), 7.04-7.09 (2H, m), 7.27-7.40 (4H, m), 7.73 (1H, s); MS (FAB) 438 (M+H, 75%), 180 (100%).

HCl salt formation. To a solution of the free base (0.77g) in diethyl ether (10ml) was added 1M-HCl in methanol (1.75ml). The solution was evaporated to dryness and on addition of diethyl ether crystals formed. The solution was filtered and the residue washed with diethyl ether to give the title compound hydrochloride salt mp 248-250°C. Found: C, 50.46; H, 3.85; N, 3.01; Cl, 7.31. $C_{20}H_{18}F_7NO_2$.HCl requires C, 50.70; H, 4.04; N, 2.96; Cl, 7.48%.

DESCRIPTION 6

4-Benzyl-3-(S)-(4-fluorophenyl)-2-(R)-(3-fluoro-5-(trifluoromethyl)benzoyloxy)morpholine

The title compound was prepared from the reaction of the compound of Description 2 with 3-fluoro-5-(trifluoromethyl)benzoyl chloride according to the procedure illustrated in Description 3. ^{1}H NMR (360MHz, $CDCl_3$) δ 2.50 (1H, dt, J=3.3, 12.0), 2.96 (1H, d, J=12.0), 2.98 (1H, d, J=13.6), 3.75 (1H, dd, J=1.7, 11.5), 3.80 (1H, d, J=2.5), 3.92 (1H, d, J=13.6), 4.19 (1H, dt, J=2.1, 12.0), 6.20 (1H, d, J=2.5), 6.99 (2H, t, J=8.7), 7.2-7.37 (5H, m), 7.51-7.55 (3H, m), 7.89 (1H, d, J=8.4), 8.09 (1H, s). MS (CI^+) m/z 478 (M^++1, 100%). Anal. Calcd. for $C_{25}H_{20}F_5NO_3$: C, 62.88; H, 4.23; N, 2.93. Found: C, 62.59; H, 4.03; N, 3.07%.

DESCRIPTION 7

4-Benzyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(3-fluoro-5-(trifluoromethyl)phenyl)ethenyloxy)morpholine

The title compound was prepared in 85% yield from the compound of Description 6 according to the procedure illustrated in Description 4. ^{1}H NMR (360MHz, $CDCl_3$) δ 2.42 (1H, dt, J=3.6, 12.0), 2.90 (1H, d, J=12.0), 2.91 (1H, d, J=13.6), 3.60-3.62 (1H, m), 3.72 (1H, d, J=2.6), 3.92 (1H, d, J=13.6), 4.09 (1H, dt, J=2.4, 12.0), 4.67 (1H, d, J=2.9), 4.76 (1H, d, J=2.9), 5.28 (1H, d, J=2.6), 7.07 (2H, t, J=8.7), 7.2-7.37 (7H, m), 7.53 (1H, s), 7.57-7.61 (2H, m). MS (CI^+) 476 (M+1, 100%).

DESCRIPTION 8

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)morpholine

The compound of Description 7 was hydrogenated according to the method illustrated in Description 5. This afforded a mixture of 2 epimeric products isomer A and isomer B (the major product) as clear oils. For the title compound: ^{1}H NMR (360MHz, $CDCl_3$) δ 1.42 (3H, d, J=6.6Hz), 1.91 (1H, s), 3.11 (1H, dd, J=3.2, 12.4Hz), 3.22 (1H, dt, J=3.6, 12.4Hz), 3.58-3.62 (1H, m), 4.01 (1H, d, J=2.3Hz), 4.11 (1H, dt, J=3.2, 12.0Hz), 4.41 (1H, d, J=2.3Hz), 4.80 (1H, q, J=6.6Hz), 6.41 (1H, d, J=9.2Hz), 6.86 (1H, s), 7.02 (2H, t, J=8.7Hz), 7.08 (2H, d, J=9.2Hz), 7.21-7.26 (2H, m). MS (CI^+) m/z 387 (M+1, 100%). Anal. Calcd. for $C_{19}H_{18}F_5NO_2$: C, 58.91; H, 4.69; N, 3.62. Found: C, 58.88; H, 4.81; N, 3.76%.

DESCRIPTION 9

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methylmorpholine

A mixture of the compound of Description 5 (1g), N,N-diacetyl-4-bromomethyl-2-imidazolinone (0.62g) (prepared according to the procedure of Dolan and Dushinsky JACS 1948, **70**, 657) and potassium carbonate (0.63g) in 10ml of dimethylformamide was stirred at room temperature for 15 min. The reaction mixture was diluted with ethyl acetate (100ml) and was washed with water and brine. The ethyl acetate layer was dried ($MgSO_4$) and evaporated *in vacuo*. The resulting oil was dissolved in ethanol (10ml), 33% ethanolic methylamine (1ml) was added and the mixture stirred at room temperature for 10 min. The mixture was concentrated *in vacuo* to afford a solid. Recrystallisation from ethyl acetate/methanol afforded the title compound (0.63g). mp 192-194°C. ^{1}H NMR (360MHz, DMSO-d_6) δ 1.35 (3H, d, J=6.5Hz), 2.25

(1H, dt, J=8.7Hz), 2.60 (1H, d, J=13.8Hz), 2.89 (1H, d, J=11.6Hz), 3.28-3.36 (2H, m), 3.62 (1H, d, J=10.2Hz), 4.1 (1H, t, J=10.0Hz), 4.31 (1H, d, J=2.7Hz), 4.92 (1H, q, J=6.5Hz), 5.97 (1H, s), 7.06 (2H, t, J=8.8Hz), 7.36 (2H, s), 7.65-7.85 (2H, m), 7.84 (1H, s), 9.58 (1H, s), 9.8 (1H, s).

DESCRIPTION 10

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-4-(2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methylmorpholine

The title compound was prepared from the compound of Description 8 using a procedure analogous to that of Description 9. mp 209-210°C. $[\alpha]_D$=+92.8 (c=1.0, methanol). ^{1}H NMR (360MHz, DMSO-d_6) δ 1.31 (3H, d, J=6.5Hz), 2.24 (1H, dt, J=3.0, 11.9Hz), 2.6 (1H, d, J=13.9Hz), 3.61 (1H, d, J=11.2Hz), 4.1 (1H, t, J=11.0Hz), 4.29 (1H, d, J=2.3Hz), 4.8 (1H, q, J=6.5Hz), 6.00 (1H, s), 6.55 (1H, d, J=9.3Hz), 6.94 (1H, s), 7.11 (2H, t, J=8.7Hz), 7.39 (1H, d, J=8.4Hz), 7.51 (2H, s), 9.59 (1H, s), 9.84 (1H, s).

DESCRIPTION 11

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine

A solution of the compound of Description 5 (3.77g) and potassium carbonate (3.59g) in dry dimethylformamide (7ml) was stirred at room temperature for 10 min. N-Formyl-2-chloroacetamidrazone (prepared according to I. Yanagisawa, *J. Med Chem.* (1984), 27, 849) was added and the reaction mixture was heated at 60°C for 1 hour. The temperature was then increased to 140°C for 2h. The mixture was cooled and partitioned

between ethyl acetate and water and the organic phase was washed with water, brine, dried ($MgSO_4$) and evaporated to give a brown oil. The residue was purified by chromatography on silica using 1-5% methanol in dichloromethane. This afforded the product as a white foam (2.99g). ^{1}H NMR (360MHz, DMSO) δ 8.25 (1H, s), 7.85 (1H, s), 7.50 (2H, t), 7.37 (2H, s), 7.11 (2H, t, J=9.0Hz), 4.93 (1H, q, J=6.6Hz), 4.32 (1H, d, J=2.8Hz), 4.09 (1H, dt, J=11.5Hz), 3.63 (1H, d, J=14.1Hz), 3.59 (1H, d, J=3.0Hz), 3.17 (1H, d, J=14.0Hz), 2.49 (1H, dt, J=15.7Hz), 1.36 (3H, d, J=6.6Hz). MS (CI^+) m/z 519. Anal. Calcd. for $C_{23}H_{19}F_7N_4O_2$: C, 53.29; H, 4.08; N, 10.81; Found: C, 52.92; H, 3.94; N, 10.33.

DESCRIPTION 12

4-Benzyl-3-(S)-(4-fluorophenyl)-2-(R)-(3-(trifluoromethyl) benzoyloxy)morpholine

The title compound was prepared from the reaction of the compound of Description 2 with 3-(trifluoromethyl)benzoyl chloride according to the procedure illustrated in Description 3. ^{1}H NMR (360MHz, $CDCl_3$) δ 2.48 (1H, dt, J=12.0, 3.5), 2.94 (1H, d, J=13.6), 3.73 (1H, app.d, J=11.4), 3.78 (1H, d, J=2.7), 3.91 (1H, d, J=13.6), 4.21 (1H, dt, J=11.7, 2.4), 6.20 (1H, d, J=2.8), 6.97 (2H, t, J=8.7), 7.25-7.37 (5H, m), 7.53 (2H, m), 7.61 (1H, t, J=7.8), 7.84 (1H, d, J=8.0), 8.21 (1H, d, J=7.8), 8.30 (1H, s). MS (CI^+) m/z 460 (M+1, 100%).

DESCRIPTION 13

4-Benzyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(3-(trifluoromethyl) phenyl)ethenyloxy)morpholine

The title compound was prepared from the compound of Description 12 according to the procedure illustrated in Description 4. ^{1}H NMR (360MHz, $CDCl_3$) δ 2.40 (1H, dt, J=11.9, 3.6Hz), 2.87 (1H, app. d, J=11.8Hz), 2.89 (1H, d, J=13.5Hz), 3.62 (1H, app.d, J=11.5Hz), 3.70 (1H, d, J=2.7Hz), 3.91 (1H, d, J=13.5Hz), 4.12 (1H, dt, J=11.7, 2.4Hz), 4.62 (1H, d, J=2.7Hz), 4.74 (1H, d, J=2.7Hz), 5.30 (1H, d, J=2.7Hz), 7.07 (2H, t, J=8.7Hz), 7.21-7.32 (5H, m), 7.40 (1H, t, J=7.8Hz), 7.53-7.63 (4H, m), 7.74 (1H, s). MS (CI^+) m/z 458 (M+1, 100%).

DESCRIPTION 14

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl) ethoxy)morpholine

The compound of Description 13 was hydrogenated according to the method illustrated in Description 5. This afforded a mixture of 2 epimeric products isomer A and isomer B in approximately equal mass as yellow oils. The title compound (isomer B): ^{1}H NMR (360MHz, $CDCl_3$) δ 1.43 (3H, d, J=6.6), 3.11 (1H, dd, J=12.6, 2.9), 3.22 (1H, dt, J=12.4, 3.7), 3.60 (1H, dd, J=11.1, 2.8), 3.99 (1H, d, J=2.2), 4.13 (1H, dt, J=11.6, 3.2), 4.42 (1H, d, J=2.2), 4.81 (1H, q, J=6.6), 6.84 (1H, d, J=7.8), 6.96-7.03 (3H, m), 7.16-7.27 (3H, m), 7.38 (1H, d, J=7.5). MS (CI^+) m/z 370 (M+1, 100%). Anal. Calcd. for $C_{19}H_{19}F_4NO_2$: C, 61.77; H, 5.20; N, 3.79. Found: C, 61.60; H, 5.16; N, 3.95%.

DESCRIPTION 15

4-Benzyl-3-(S)-phenyl-2-morpholinone

Step A: N-Benzyl-(S)-phenylglycine

A solution of 1.51g (10.0mmol) of (S)-phenylglycine in 5ml of 2N aqueous sodium hydroxide solution was treated with 1.0ml (10.0mmol) of benzaldehyde and stirred at room temperature for 20 minutes. The solution was diluted with 5ml of methanol, cooled to 0°C, and carefully treated with 200mg (5.3mmol) of sodium borohydride. The cooling bath was removed and the reaction mixture was stirred at room temperature for 1.5 hours. The reaction was diluted with 20ml of water and extracted with 2 x 25ml of methylene chloride. The aqueous layer was acidified with concentrated hydrochloric acid to pH 6 and the solid that precipitated was filtered, washed with 50ml of water, 50ml of 1:1 v/v methanol/ethyl ether and 50ml of ether, and dried to afford 1.83g (76%) of product, mp 230-232°C. Anal. Calcd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.17; H, 6.19; N, 5.86.

Step B: 4-Benzyl-3-(S)-phenyl-2-morpholinone

A mixture of 4.00g (16.6mmol) of N-benzyl-(S)-phenylglycine (from Step A) 5.00g (36.0mmol) of potassium carbonate, 10.0ml of 1,2-dibromoethane and 25ml of N,N-dimethylformamide was stirred at 100°C for 20 hours. The mixture was cooled and partitioned between 200ml of ethyl ether and 100ml of water. The layers were separated and the organic layer was washed with 3 x 50ml of water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by flash chromatography on 125g of silica gel eluting with 9:1 v/v, then 4:1 hexanes/ethyl ether to afford 2.41g (54%) of the product as a solid, mp 98-100°C. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.54-2.68 (1H, m), 2.96 (1H, dt, J=12.8, 2.8), 3.14 (1H, d, J=13.3), 3.75 (1H, d, J=13.3), 4.23 (1H, s), 4.29-4.37 (1H, m), 4.53

(dt, J=3.2, 11.0), 7.20-7.56 (10H, m). MS (FAB): m/z 268 (M+H; 100%). Anal. Calcd for $C_{17}H_{17}NO_2$: C, 76.38; H, 6.41; N, 5.24. Found: C, 76.06; H, 6.40; N, 5.78.

DESCRIPTION 16

4-Benzyl-2-(R)-(3,5-bis(trifluoromethyl)benzoyloxy)-3-(S)-phenylmorpholine

A solution of 2.67g (10.0mmol) of the compound of Description 15 in 40ml of dry THF was cooled to -78°C. The cold solution was treated with 12.5ml of 1.0M L-Selectride® solution in THF, maintaining the internal reaction temperature below -70°C. The resulting solution was stirred cold for 45 minutes and the reaction was charged with 3.60ml (20.0mmol) of 3,5-bis(trifluoromethyl) benzoyl chloride. The resulting yellow mixture was stirred cold for 30 minutes and the reaction was quenched with 50ml of saturated aqueous sodium bicarbonate solution. The quenched mixture was partitioned between 300ml of ether and 50ml of water and the layers were separated. The organic layer was dried over magnesium sulfate. The aqueous layer was extracted with 300ml of ether; the extract was dried and combined with the original organic layer. The combined organics were concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 37:3 v/v hexanes/ether as the eluant afforded 4.06g (80%) of the title compound as a solid. ^{1}H NMR (200MHz ppm, $CDCl_3$) δ 2.50 (1H, dt, J=3.4, 12.0), 2.97 (1H, app d, J=12.0), 2.99 (1H, d, J=13.6), 3.72-3.79 (1H, m), 3.82 (1H, d, J=2.6), 4.00 (1H, d, J=13.6), 4.20 (dt, J=2.4, 11.6), 6.22 (1H, d, J=2.6), 7.22-7.37 (7H, m), 7.57 (2H, app d, J=6.8), 8.07 (1H, s), 8.47 (2H, s). Anal. Calcd for $C_{26}H_{21}F_6NO_3$: C, 61.29; H, 4.16; N, 2.75; F, 22.38. Found: C, 61.18; H, 4.14; N, 2.70; F, 22.13.

DESCRIPTION 17

4-Benzyl-2-(R)-(1-(3,5-bis(trifluoromethyl)phenyl) ethenyloxy)-3-(S)-phenylmorpholine

A solution of 2.50g (4.9mmol) of the compound of Description 16 and 2.50g (12.0mmol) of dimethyl titanocene (Description 4a), in 35ml of 1:1 v/v THF/toluene was stirred in an oil bath at 80°C for 16 hours. The reaction mixture was cooled and concentrated *in vacuo*. Flash chromatography on 150g of silica gel using 3:1 v/v hexanes/methylene chloride as the eluant afforded 1.71g (69%) of the title compound as a solid. ^{1}H NMR (400MHz, $CDCl_3$) δ 2.42 (1H, dt, J=3.6, 12.0), 2.89 (app d, J=11.6), 2.92 (1H, d, J=13.6), 3.61-3.66 (1H, m), 3.73 (1H, d, J=2.8), 4.00 (1H, d, J=13.6), 4.09 (1H, dt, J=2.4, 11.6), 4.75 (1H, d, J=2.8), 4.79 (1H, d, J=2.8), 5.36 (1H, d, J=2.4), 7.23-7.41 (7H, m), 7.63 (1H, app d, J=7.2), 7.79 (1H, s), 7.91 (2H, s). MS (FAB) m/z 508 (M+1, 25%). Anal. Calcd. for $C_{27}H_{23}F_6NO_2$: C, 63.90; H, 4.57; N, 2.76; F, 22.46. Found: C, 63.71; H, 4.53; N, 2.68; F, 22.66.

DESCRIPTION 18

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenylmorpholine

A mixture of the compound of Description 17 (1.5g) and 10% palladium on carbon catalyst (750mg) in a mixture of isopropanol/ethyl acetate (25ml, 3:2 v/v) was stirred under an atmosphere of hydrogen for 48h. The catalyst was removed by filtration through celite and the reaction flask and filter pad were rinsed with ethyl acetate (500ml). The filtrate was concentrated *in vacuo*, flash chromatography afforded epimer A (106mg) and

epimer B (899mg) as clear oils. The title compound, epimer B had the following analysis:

^{1}H NMR ($CDCl_3$, 400MHz) δ 1.46 (3H, d, J=6.8Hz), 1.92 (1H, brs), 3.13 (1H, dd, J=3.0, 12.6Hz), 3.24 (1H, dt, J=3.6, 12.6Hz), 3.62 (1H, dd, J=3.6, 11.2Hz), 4.04 (1H, d, J=2.4Hz), 4.14 (1H, dt, J=3.0, 11.2Hz), 4.48 (1H, d, J=2.4Hz), 4.90 (1H, q, J=6.8Hz), 7.21-7.32 (7H, m), 7.64 (1H, s). MS (CI^+) m/z 420 (M^++1, 20%), 178 (100%). Anal. Calcd. for $C_{20}H_{19}F_6NO_2$: C, 57.28; H, 4.57; N, 3.34; F, 27.18. Found: C, 57.41; H, 4.61; N, 3.29; F, 27.23.

DESCRIPTION 19

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(1,2,4-triazol-3-yl)methylmorpholine

This compound was prepared from the compound of Description 18 following the procedure illustrated in Description 11. MS (CI^+) m/z 501 (M^++1, 100%).

DESCRIPTION 20

4-Benzyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 4 (12.8g) was dissolved in tetrahydrofuran (50ml) and the mixture was cooled in ice. Borane (49ml of 1.0M in tetrahydrofuran) was added dropwise and the reaction mixture was stirred at room temperature for 3hr. The solution was cooled in ice and sodium hydroxide (120ml, 1M) and hydrogen peroxide (36ml, 30 wt. %) were added dropwise cautiously. The resulting mixture was stirred for 1h, then diluted with water (200ml) and extracted with ethyl acetate (3 x 50ml). The organic extracts were washed with sodium sulfite and then brine.

The organic phase was dried ($MgSO_4$) and evaporated to give a clear oil. Tlc (50:50 ethyl acetate/hexane) indicated two main products which were separated by flash chromatography on silica using a gradient elution of 1-30% ethyl acetate in hexane. The minor product eluted first (2.3g) and the major product eluted last (8g). The major product was isolated as a white foam. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.23-2.29 (1H, m), 2.73 (1H, d), 2.80 (1H, d, J=13.0Hz), 3.48 (1H, d, J=3.5Hz), 3.45-3.52 (2H, m), 3.56-3.65 (2H, m), 4.00-4.06 (1H, m), 4.37 (1H, d, J=3.0Hz), 4.81 (1H, t, J=6.0Hz), 4.92 (1H, t, J=5.5Hz), 7.14 (2H, t, J=9.0Hz), 7.23-7.33 (5H, m), 7.35 (2H, s, ArH), 7.57 (2H, t, ArH), 7.85 (1H, s, ArH). MS (CI$^+$) m/z 544 (M$^+$+1, 100%).

DESCRIPTION 21

2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 20 (8g) was dissolved in ethyl acetate (100ml) and isopropanol (50ml) and palladium on charcoal (1.5g) was added to the solution. This mixture was hydrogenated at 40 psi overnight. The catalyst was removed by filtration and the solvents were removed *in vacuo*. The residue was purified by flash silica chromatography using 1-10% methanol in dichloromethane as eluant. This afforded the product as a white powder (5.7g, 90%). ^{1}H NMR (360MHz, $CDCl_3$) δ 2.68-2.73 (1H, m), 3.03-3.15 (1H, m), 3.43-3.65 (3H, m), 3.95 (1H, d, J=3.0Hz), 4.12-4.22 (1H, m), 4.40 (1H, d, J=3.0Hz), 4.89 (1H, t, J=7.0Hz), 6.99 (t, J=9.0Hz, ArH), 7.15 (2H, s, ArH), 7.26-7.31 (1H, m, ArH), 7.62 (1H, s, ArH). MS (CI$^+$) m/z 454 (M$^+$+1, 100%).

DESCRIPTION 22

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

Step A: 4-Benzyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

The compound of Description 7 (0.8g) was dissolved in tetrahydrofuran (5ml) at room temperature and borane (5ml, 1.0M in tetrahydrofuran) was added. The solution was stirred under nitrogen for 30 min until all starting material had reacted. Hydrogen peroxide (5ml, 29% aq.) and sodium hydroxide (10ml, 4N) were added dropwise to the cooled (0°C) solution with much effervescence. The resulting mixture was extracted with ethyl acetate, the organic phase was washed with sodium bisulfite and brine, dried ($MgSO_4$) and evaporated to afford a colourless oil (1g). This material was not purified further but reacted as described in the following step.

Step B: 3-(S)-(4-Fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

The compound of (a) above (1g) was dissolved in ethyl acetate/2-propanol (20ml, 3:1) and treated with Pd on carbon (100mg). The mixture was hydrogenated at 60 psi for 12h. The catalyst was removed by filtration and the solvent was removed *in vacuo*. The residue was purified by medium pressure chromatography on silica (Lobar) using 5% methanol in dichloromethane as eluant. The product was recrystallised from ether. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.77-3.04 (3H, m), 3.36-3.51 (2H, m), 3.93 (1H, br s), 4.05-4.13 (1H, m), 4.36 (1H, d, J=2.0Hz),

4.72 (1H, t, J=5.0Hz), 4.98 (1H, t, J=7.0Hz), 6.66 (1H, d, J=9.2Hz), 6.89 (1H, s), 7.10 (2H, t, J=9.0Hz), 7.33-7.37 (2H, m), 7.41 (1H, d, J=9.0Hz); MS (CI^+) m/z 404 (M^++1, 100).

DESCRIPTION 23

N-Carbomethoxy-2-chloroacetamidrazone

($ClCH_2C(=NH)NHNHCOOCH_3$)

Sodium methoxide (20ml, 1M) was added to a solution of chloroacetonitrile (54.1g) in anhydrous methanol (100ml) at 0°C. The mixture was stirred at room temperature for 30 min and then neutralised with acetic acid (1.2ml). Methyl hydrazinocarboxylate (64.5g, predistilled *in vacuo*) was dissolved in warm dimethylformamide (35ml) and methanol (300ml) and was added to the reaction mixture at 0°C. The mixture was stirred for 30 min and the crystalline solid which had formed was removed by filtration and washed with ethyl acetate to give the title compound: mp 138-140°C.

DESCRIPTION 24

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

Step A: 4-Benzyl-2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

The compound of Description 17 was reacted with diborane and subsequently with basic hydrogen peroxide according to the method illustrated in Description 20. This intermediate was not purified and was reacted crude in the following step.

Step B: 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl-2-hydroxyethoxy)-3-(S)-phenylmorpholine

The compound of (a) above was deprotected by hydrogenolysis as described in Description 21 to afford the title compound as a white solid. ^1H NMR (360MHz, $CDCl_3$) δ 2.85 (1H, app d, J=11.0Hz), 3.15 (1H, dt, J=12.0, 3.5Hz), 3.58 (1H, dd, J=11.0, 3.0Hz), 3.63-3.71 (2H, m), 4.02 (1H, d, J=3.0Hz), 4.25 (dt, J=12.0, 3.0Hz), 4.53 (1H, d, J=3.0Hz), 4.93 (1H, t, J=5.0Hz), 7.22 (2H, s), 7.35 (5H, br s), 7.67 (1H, s). MS (CI^+) m/z 436 (M+1, 100%).

DESCRIPTION 25

4-Benzyl-2-(R)-(3-fluoro-5-(trifluoromethyl)benzoyloxy)-3-(S)-phenylmorpholine

The compound of Description 15 was reacted with L-Selectride followed by 3-fluoro-5-(trifluoromethyl)benzoyl chloride according to the method illustrated in Description 3 to afford the title compound as a clear oil. ^1H NMR (250MHz, $CDCl_3$) δ 2.47 (1H, dt, J=8.5, 2.5Hz), 2.93-2.97 (2H, m), 3.72-3.76 (1H, m), 3.79 (1H, d, J=3.0Hz), 3.97 (1H, d, J=9.5Hz), 4.17 (1H, dt, J=8.5, 2.5Hz), 6.22 (1H, d, J=3.0Hz), 7.19-7.35 (8H, m), 7.45-7.56 (3H, m), 7.88 (1H, brd), 8.09 (1H, s). MS (CI^+) m/z 460 (M+1, 100%).

DESCRIPTION 26

4-Benzyl-2-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethenyloxy)-3-(S)-phenylmorpholine

The compound of Description 25 was reacted with dimethyl titanocene according to the procedure illustrated in Description 4. This afforded the title compound as a clear oil (66%). ^1H NMR (250MHz, $CDCl_3$) δ 2.29-2.39 (1H, m), 2.79-2.86 (2H, m), 3.53-3.64

(2H, m), 3.92 (1H, d, J=13.5Hz), 4.00-4.09 (1H, m), 4.61 (1H, d, J=3.0Hz), 4.66 (1H, d, J=3.0Hz), 5.25 (1H, d, J=3.0Hz), 7.14-7.35 (10H, m), 7.47 (1H, s), 7.56 (2H, brd). MS (CI^+) m/z 458 (M+1, 100%).

DESCRIPTION 27

2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

Step A: 4-Benzyl-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

The compound of Description 26 was reacted with diborane followed by treatment with basic hydrogen peroxide according to the procedure illustrated in Description 20 to afford a clear oil. MS (CI^+) m/z 476 (M+1, 100%).

Step B: 2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

The compound of (a) above was deprotected following the method illustrated in Description 21. This afforded the title compound as a white solid. Anal. Calcd. for $C_{19}H_{19}F_4NO_3$: C, 59.22; H, 4.97; N, 3.63. Found: C, 59.18; H, 5.12; N, 3.62%. MS (CI^+) m/z 386 (M+1, 100%).

DESCRIPTION 28

4-Benzyl-3-(S)-phenyl-2-(R)-(3-(trifluoromethyl)benzoyloxy)morpholine

Prepared from the compound of Description 15 following the method illustrated in Description 3. ^1H NMR (250MHz, $CDCl_3$) δ

2.47 (1H, dt), 2.89-2.99 (2H, m), 3.69-3.82 (2H, m), 3.98 (1H, d), 4.23 (1H, dt), 6.22 (1H, d), 7.22-7.40 (8H, m), 7.54-7.66 (3H, m), 7.83 (1H, d), 8.22 (1H, d), 8.31 (1H, s).

DESCRIPTION 29

4-Benzyl-3-(S)-phenyl-2-(R)-(1-(3-trifluoromethyl)phenyl) ethenyloxy)morpholine

Prepared from the compound of Description 28 following the method illustrated in Description 4. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.41 (1H, dt), 2.84-2.96 (2H, m), 3.58-3.66 (1H, m), 3.72 (1H, d, 3.99 (1H, d), 4.13 (1H, dt), 4.63 (1H, d), 4.72 (1H, d), 5.34 (1H, d), 7.21-7.43 (9H, m), 7.50-7.68 (4H, m), 7.75 (1H, s).

DESCRIPTION 30

3-(S)-Phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

Step A: 4-Benzyl-3-(S)-phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

Prepared from the compound of Description 29 following the method illustrated in Description 20.

Step B: 3-(S)-Phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

This was carried through without purification to the title compound following the method illustrated in Description 21. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.81-2.90(1H, br d), 3.16 (1H, dt), 3.54-3.68 (3H, m), 4.02 (1H, d), 4.28 (1H, dt), 4.53 (1H, d), 4.85-4.92

(1H, m), 6.85 (1H, d), 6.99 (1H, s), 7.15-7.24 (1H, m), 7.34-7.45 (6H, m).

EXAMPLE 1

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(2,3-dihydro-5-(N,N-dimethylaminomethyl)-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 9 (0.35g) was treated with N,N-dimethylmethyleneammonium iodide (0.48g) and triethylamine (111μl) in tetrahydrofuran (10ml) and the mixture was heated at reflux for 4h. The solvent was removed *in vacuo* and the residue was purified by chromatography on silica using 1-10% methanol in dichloromethane as eluant to afford the title compound (0.2g). ^1H NMR (250MHz, $CDCl_3$) δ 9.72 (1H, s), 9.68 (1H, s), 7.86 (1H, s), 7.50-7.60 (2H, m), 7.36 (2H, s), 7.07 (2H, t, J=8.8Hz), 4.96-4.89 (1H, q, J=6.5Hz), 4.31 (1H, d, J=2.7Hz), 4.08 (1H, t, J=10.1Hz), 3.62 (1H, d, J=10.1Hz), 3.34 (2H, s), 3.24 (1H, d, J=13.6Hz), 3.00 (1H, d, J=13.4Hz), 2.85 (1H, d, J=11.1Hz), 2.62 (1H, d, J=13.6Hz), 2.25 (1H, t, J=11Hz), 2.01 (6H, s), and 1.35 (3H, d, J=6.5Hz). MS (CI^+) m/z 591 (M+1).

EXAMPLE 2

4-(2,3-Dihydro-5-(N,N-dimethylaminomethyl)-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)morpholine

Prepared from the compound of Description 10 by a procedure analogous to that of Example 1. ^1H NMR (250MHz, $CDCl_3$) δ 1.38 (3H, d, J=6.2Hz), 2.22 (6H, s), 2.78 (1H, d, J=14Hz), 2.92 (1H, d, J=11.2Hz), 3.14 (2H, app. q, J=14Hz), 3.34 (1H, d, J=2.8Hz), 3.46

(1H, d, J=11.2Hz), 3.60 (1H, d, J=10Hz), 4.22 (2H, m), 4.26 (1H, d, J=2.8Hz), 4.74 (1H, q, J=6.2Hz), 6.32 (1H, d, J=8.4Hz), 6.72 (1H, s), 7.06 (3H, t, J=8.4Hz), 7.36 (2H, br s), 8.70 (1H, br s), 9.20 (1H, br s).

EXAMPLE 3

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine

A mixture of the compound of Description 10, (0.1g), paraformaldehyde (0.012g) and pyrrolidine (0.04ml) in methanol (2ml) was heated at 90°C for 1h. An additional aliquot of paraformaldehyde (12mg) was added to the mixture and heating was continued for a further 30 min. The mixture was cooled and the solvent was removed *in vacuo*. The residue was purified by chromatography on silica using 0.5% aqueous ammonia and 5% methanol in dichloromethane. This afforded the product as a foam. The product was further purified as the hydrochloride salt: mp 157-9°C. ^{1}H NMR (250MHz, (free base) $CDCl_3$) δ 1.40 (3H, t, J=6.2Hz), 1.72 (4H, br s), 2.41 (4H, br s), 2.76 (1H, d, J=12.9Hz), 2.92 (1H, d, J=11.2Hz), 3.14-3.50 (5H, m), 3.62 (1H, d, J=11.2Hz), 4.16 (1H, d, J=12.9Hz), 4.26 (1H, d, J=2.8Hz), 4.71 (1H, q, J=6.2Hz), 6.30 (1H, d, J=8.4Hz), 6.75 (1H, s), 7.06 (3H, t, J=8.4Hz), 7.34 (2H, br s), 8.86 (1H, br s), 9.14 (1H, br s). MS (CI$^+$) m/z 567 (M$^+$+H).

EXAMPLE 4

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine

A solution of the compound of Description 5 (1.5g) in anhydrous dimethylformamide (15ml) was added dropwise during 5 min to a stirred solution of 4,5-bis(bromomethyl)-1,3-diacetyl-2-imidazolinone (1.8g) (prepared by the method of Dolan and Dushinsky *JACS* (1948) 70, 657) in dimethylformamide (10ml) containing potassium carbonate (1.4g) with ice-cooling. The reaction mixture was stirred for 10 min and pyrrolidine (1.1g) was added in one portion and stirring was continued for 20 min. The reaction mixture was diluted with water (250ml) and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with water (2 x 50ml) and brine (1 x 50ml) and then dried (K_2CO_3) and concentrated *in vacuo*. The residue was purified by chromatography on silica using a gradient elution of dichloromethane (100%) to dichloromethane/methanol/aqueous ammonia mixtures (85:15:0.5) to provide the title compound as a foam. ^{1}H NMR (360MHz, DMSO-d_6) δ 9.63 (2H, br s), 7.84 (1H, s), 7.53 (2H, br t), 7.36 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.94-4.90 (1H, q, J=6.5Hz), 4.31 (1H, d, J=2.68Hz), 4.07 (1H, t, J=11.4Hz), 3.61 (1H, d, J =11.20Hz), 3.34 (1H, J=2.7Hz), 3.27 (1H, d, J=13.7Hz), 3.17 (1H, d, J=13.4Hz), 3.00 (1H, d, J=13.4Hz), 2.86 (1H, d, J=11.6Hz), 2.62 (1H, d, J=13.6Hz), 2.40-2.20 (5H, m), 1.64-1.58 (2H, m), 1.35 (3H, d, J=6.5Hz). MS (CI^+) m/z 615 (M^++H).

Examples 5 to 11 in Table 1 were prepared in a similar manner to that described in Example 4 from the appropriate morpholine, 4,5-bis(bromomethyl)-1,3-diacetyl-2-imidazolinone and the appropriate amine.

EXAMPLE 12

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

Method A

a) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy-3-(S)-(4-fluorophenyl)-4-propargylmorpholine

Propargyl bromide (1.9ml) was added to a stirred mixture of the compound of Description 5 (5g) and potassium carbonate (4.76g) in dry dimethylformamide at 23°C. After 15 min the reaction mixture was diluted with water (250ml) and extracted with ethyl acetate (3 x 100ml). The combined organic phases were washed with brine (1 x 100ml) then dried (K_2CO_3) and concentrated to leave an oil. This was purified by chromatography on silica using ethyl acetate in hexane (1:9 then 1:4) as eluent to afford the title compound as an oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 1.50 (3H, d, J=6.6Hz), 2.21 (1H, s), 2.84 (1H, d, J=11.1Hz), 2.97 (1H, td, J=3.2, 11.7Hz), 3.26 (2H, d, J=1.8Hz), 3.62 (1H, d, J=2.2Hz), 3.71 (1H, dd, J=2.3, 11.1Hz), 4.33 (2H, m), 4.89 (1H, q, J=6.6Hz), 7.03 (2H, t, J=8.6Hz), 7.18 (2H, s), 7.38 (2H, br s), 7.63 (1H, s). MS (CI^+) m/z 476 (MH, 100%).

b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-dimethylamino-4-oxo-but-2-ynyl)-3-(S)-(4-fluorophenyl)morpholine

A mixture of N,N-dimethylcarbamoyl chloride (0.195ml), cuprous iodide (2mg), bis(triphenylphosphine)palladium (II) chloride (2mg), triphenylphosphine (3mg) and the compound described in (a) above (1g) in triethylamine (4ml) was heated at 90°C for 5h in an inert atmosphere. The mixture was cooled to 23°C and methanol (1ml) was added and the solvent was removed *in vacuo*. The residue

was partitioned between water and ethyl acetate and the layers were separated. The aqueous phase was extracted with ethyl acetate (2 x 20ml). The combined organic phases were washed with water, brine, dried ($MgSO_4$) and concentrated to leave an oil. The residue was purified by chromatography on silica using ethyl acetate in hexane (1:1) then ethyl acetate as eluant to provide the title compound as an oil. ^1H NMR (250MHz, $CDCl_3$) δ 1.49 (3H, d, J=6.6Hz), 2.84-3.06 (2H, m), 3.00 (3H, s), 3.17 (3H, s), 3.44 (2H, s), 3.64 (1H, br s), 3.73 (1H, dd, J=2.0, 11.1Hz), 4.33 (2H, m), 4.88 (1H, q, J=6.6Hz), 7.03 (2H, t, J=8.7Hz), 7.17 (2H, s), 7.38 (2H, br s), 7.63 (1H, s). MS (CI^+) m/z 547 (MH, 100%).

c) <u>2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N,N-dimethylcarboxamido-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine</u>

A mixture of the compound described in (b) above (1.1g) and sodium azide (0.65g) in dimethylsulphoxide (7.5ml) was heated at 70°C for 17h. The mixture was cooled to 23°C and excess dimethylsulphoxide was removed by distillation *in vacuo*. The residue was partitioned between brine and ethyl acetate. The layers were separated and the organic layer was washed with brine (2 x 20ml) then dried ($MgSO_4$) and concentrated to leave an oil. This was purified by chromatography on silica using ethyl acetate in hexane (1:2 then 1:1) and then ethyl acetate as eluent to provide the title compound as a pale yellow foam. ^1H NMR (360MHz, $CDCl_3$) δ 1.47 (3H, d, J=6.6Hz), 2.64 (1H, m), 2.90 (1H, d, J=11.6Hz), 3.09 (3H, s), 3.34 (3H, s), 3.65 (3H, m), 3.92 (1H, d, J=15.5Hz), 4.27 (1H, td, J=2.1, 9.5Hz), 4.35 (1H, d, J=2.6Hz), 4.89 (1H, q, J=6.6Hz),

7.01 (2H, t, J=8.7Hz), 7.16 (2H, s), 7.39 (2H, br s), 7.64 (1H, s). m/z 590 (MH, 100%).

d) 2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

Lithium aluminium hydride (0.47ml, 1M in tetrahydrofuran) was added dropwise to a solution of the compound described in (c) above (0.11g) in dry tetrahydrofuran (1ml) under an inert atmosphere at 23°C. After 30 min sodium hydroxide (10 drops, 1M) was added followed by water (5 drops). Ethyl acetate (50ml) was then added and the resulting mixture was filtered through a pad of Hyflo. The filtrate was concentrated *in vacuo* and the residue was purified by chromatography on silica using ethyl acetate in methanol (9:1 then 4:1) as eluant to provide the title compound as a foam. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 2.25 (6H, s), 2.57 (1H, td, J=3.4, 8.55Hz), 2.90 (1H, d, J=11.7Hz), 3.25 (1H, d, J=14.0Hz), 3.43 (1H, d, J=13.6Hz), 3.45 (1H, d, J=2.2Hz), 3.53 (1H, d, J=13.6Hz), 3.61 (1H, d, J=11.2Hz), 3.78 (1H, d, J=14.0Hz), 4.22 (1H, t, J=9.3Hz), 4.32 (1H, d, J=2.2Hz), 4.86 (1H, q, J=6.6Hz), 7.06 (2H, t, J=8.7Hz), 7.16 (2H, s), 7.48 (2H, br s), 7.63 (1H, s). m/z 576 (MH).

Method B

2-(R)-1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-chlorobut-2-ynyl)morpholine

a) A solution of the product of Description 5 (free base, 5g) in N,N-dimethylformamide (20ml) was slowly added to a heated (50°C) solution of 1,4-dichlorbut-2-yne (2.2ml) and potassium

carbonate (4.8g) in N,N-dimethylformamide (20ml). The solution was heated for a further 5h at 50°C and then the solvent removed *in vacuo*. To the residue was added water (400ml) and the product extracted into ethyl acetate (3 x 150ml). The combined organic phase washed with water, saturated brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue chromatographed on silica gel (eluting with 10% ethyl acetate in petroleum ether bp 60-80°C) to give the title compound. ^{1}H NMR (250MHz, $CDCl_3$) δ 1.41 (3H, d, J=6.6Hz), 2.80 (1H, app. t, J=10.8Hz), 2.87 (1H, td, J=3.5Hz, 11.7Hz), 3.22 (2H, t, J=1.9Hz), 3.52 (1H, d, J=2.8Hz), 3.68 (1H, d, J=1.4Hz, 11.1Hz), 4.00 (2H, t, J=1.9Hz), 4.22-4.32 (2H, m), 4.81 (1H, q, J=6.6Hz), 6.96 (2H, t, J=8.7Hz), 7.10 (2H, s), 7.31 (2H, br s), 7.56 (1H, s). m/z (CI^+) 524 (M+H, 100%).

b) <u>N-(4-Azidobut-2-ynyl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine</u>

To a solution of 2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-chlorobut-2-ynyl)morpholine (4g) in dimethyl sulphoxide (17ml) was added sodium azide (0.562g). The solution was stirred for 20h and aqueous ammonium chloride and ethyl acetate were added. The organic phase was washed with water (2 times), saturated brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue chromatographed on silica gel (eluting with 20% ethyl acetate in petroleum ether bp 60-80°C) to give the title compound. ^{1}H NMR (360MHz, $CDCl_3$) δ 1.48 (3H, s, J=6.6Hz), 2.87 (1H, app t, J=10.2Hz), 2.98 (1H, td, J=3.6, 11.7Hz), 3.35 (2H, t, J=1.9Hz), 3.61 (1H, d, J=2.8Hz), 3.72 (1H, dq, J=1.4Hz, 10.0Hz), 3.92 (2H, t,

J=1.9Hz), 4.30-4.40 (2H, m), 4.89(1H, q, J=6.6Hz), 7.03 (2H, t, J=8.7Hz), 7.17 (2H, s), 7.27 (2H, br s), 7.63 (1H, s).

c) <u>2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine</u>

Dimethylamine (approximately 10ml) was condensed at -80°C in a pressure tube and to this was added a solution of N-(4-azidobut-2-ynyl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl) ethoxy)-3-(S)-(4-fluorophenyl)morpholine (3.2g) in dioxan (15ml). The tube was sealed and the solution was heated at 90°C for 16h. The solution was evaporated to dryness and the residue chromatographed on silica gel (eluting with 5% methanol in dichloromethane containing 0.25% ammonia (SG. 0.88)) and the fractions containing the desired product were evaporated *in vacuo* to give the title compound. To a solution of this residue in diethyl ether was added 1M-HCl in methanol. The solution was evaporated to dryness and redissolved in diethyl ether to give crystals of <u>the title compound hydrochloride salt</u> m.p. 194-198°C, $[\alpha]^{22}_D$ + 65.0° (c=0.5, H_2O). The crystals were found to be stable for at least five days at 40°C; at 40°C/75% relative humidity; at 80°C; and at 2000LUX.

<u>EXAMPLE 13</u>

<u>2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-(2-methylaminoethyl)-1,2,4-triazol-3-yl)methylmorpholine: Regioisomer B</u>

a) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(N-carbomethoxymethyl-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

The compound of Description 11 (2.94g), potassium carbonate (2.03g) and methyl bromoacetate (0.74ml) were heated for 45 min in dimethylformamide. The reaction was partitioned between ethyl acetate and water, washed (brine), dried ($MgSO_4$) and purified on silica using petrol-ethyl acetate mixtures. Two products, isomer A and isomer B were obtained as white foams.

Isomer A: ^{1}H NMR (360MHz, DMSO) δ 7.89 (1H, s), 7.84 (1H, s), 7.48 (3H, s), 7.33-7.30 (3H, m, J=10.1), 5.26 (1H, d, J=17.8), 5.07 (1H, d, J=17.8), 4.96 (1H, q, J=6.5), 4.39 (1H, d, J=2.8), 4.04 (1H, br t, J=10.1Hz), 3.72 (3H, s), 3.58 (2H, d, J=14.0), 3.51 (1H, d, J=2.8), 3.20 (1H, d, J=14.0), 2.55 (1H, d, J=11.5), 2.37 (1H, br t, J=3.5), 1.40 (3H, d, J=6.6).

Isomer B: ^{1}H NMR (360MHz, DMSO) δ 8.43 (1H, s), 7.82 (1H, s), 7.44 (2H, d, J=1.4), 7.37 (2H, s), 7.31-7.25 (3H, m, J=3.2), 5.16 (2H, s), 4.91 (1H, q, J=6.5), 4.35 (1H, d, J=2.8), 4.08 (1H, br t, J=10.1), 3.69 (3H, s), 3.60 (1H, d, J=8.8), 3.55 (1H, d, J=2.7), 3.30 (1H, d, J=8.7), 3.08 (1H, d, J=13.7), 2.95 (1H, d, J=11.5), 2.47 (1H, br t, J=3.4), 1.35 (3H, d, J=6.5). MS (CI^+) m/z 573 (M+1).

b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-(N'-methylcarboxamido)methyl-1,2,4-triazol-3-yl)methylmorpholine

Monomethylamine gas was bubbled through a solution of the compound of (a) above (375mg Isomer b) in methanol (25ml) for 10 min and then sealed for 16h. Reaction mixture was evaporated, redissolved in ethyl acetate and concentrated *in vacuo* to a white

solid (374mg). ^{1}H NMR (250MHz, $CDCl_3$) δ 8.09 (1H, s), 7.61 (1H, s), 7.45 (2H, br s), 7.33 (2H, s), 7.31 (1H, br s), 7.13 (2H, br s), 4.85 (1H, q, J=6.5Hz), 4.76 (2H, s), 4.37 (1H, br s), 4.36 (1H, br s), 3.85 (1H, d), 3.66 (1H, br s), 3.63 (1H, br s), 3.49 (1H, d), 3.03 (1H, br s), 2.82 (3H, d), 2.80 (1H, br s), 1.46 (3H, d). MS (CI^+) 573 (M^++1).

c) <u>2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-(2-methylaminoethyl)-1,2,4-triazol-3-yl)methylmorpholine</u>

A cooled solution of the compound of (b) above (302mg) in tetrahydrofuran (5ml) and borane-tetrahydrofuran complex (1.59ml, 1M) was stirred for 60 min before heating (60°C) for a further 60 min. The reaction was evaporated and redissolved in CH_3OH with K_2CO_3 before heating to reflux for 30 min. The reaction was poured into ethyl acetate, washed (water x 2, brine), dried ($MgSO_4$). Purification on silica using CH_3OH-dichloromethane mixtures gave the title compound as colourless oil (54mg). ^{1}H NMR (250MHz, $CDCl_3$) δ 7.97 (1H, s), 7.53 (1H, s), 7.39 (2H, br s), 7.29-7.23 (3H, m, J=2.6), 7.06 (2H, s), 4.77 (1H, q, J=6.6), 4.29 (1H, d, J=2.9), 4.25 (1H, br t, J=2.6), 4.13 (2H, t, J=5.7), 3.76 (1H, d, J=14.2), 3.57 (1H, t, J=3.5), 3.53 (1H, d, J=2.8), 3.31 (1H, d, J=14.1), 2.95 (1H, t, J=9.3), 2.92 (2H, t, J=5.9), 2.56 (1H, br t, J=3.5), 2.36 (3H, s), 2.16 (1H, br s), 1.37 (3H, d, J=6.6). MS (CI^+) m/z 558 (M^++1).

Examples 14 to 21 in Table 2 were prepared in a similar manner to that described in Example 12, Method B, via the appropriate N-(4-azidobut-2-ynyl)morpholine and the appropriate amine.

EXAMPLE 22

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(1-(2-pyrrolidinoethyl)-1,2,4-triazol-3-yl)methylmorpholine

a) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(1-(2-oxo-2-pyrrolidinoethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-phenylmorpholine

A solution of the compound of Description 19 (2.86g), potassium carbonate (2.37g) and l-bromoacetylpyrrolidine (1.21g) was heated at 60°C in dimethylformamide (15ml). The mixture was cooled and partitioned between water and ethyl acetate. The organic phase was washed with water, brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the residue was purified on silica using 1.5% methanol in dichloromethane as eluent. This afforded 2 products isomer A and isomer B.

Isomer A (Alkylation at 2 position of 1,2,4-triazole): ^{1}H NMR (250MHz, $CDCl_3$) δ 7.83 (1H, s), 7.61 (1H, s), 7.39-7.30 (5H, m), 7.16 (2H, s), 5.00 (1H, d, J=16.4Hz), 4.88 (1H, q, J=6.6Hz), 4.67 (1H, d, J=16.4Hz), 4.35 (1H, d, J=2.8Hz), 4.20 (1H, br t, J=11.6Hz), 3.77 (1H, d, J=14.4Hz), 3.62 (1H, dd, J=11.3Hz), 3.51-3.44 (4H, m), 3.39 (1H, s), 3.33 (1H, d, J=14.4Hz), 2.90 (1H, d, J=11.4Hz), 2.74 (1H, br t, J=11.8Hz), 2.12-2.02 (2H, m), 1.97-1.86 (2H, m), 1.45 (3H, d, J=6.6Hz).

Isomer B (Alkylation at 1 position of 1,2,4-triazole). ^{1}H NMR (250MHz, $CDCl_3$) δ 8.19 (1H, s), 7.60 (1H, s), 7.47 (2H, br s), 7.36-7.27 (3H, m), 7.14 (2H, s), 4.89 (2H, s), 4.85 (1H, q, J=6.6Hz), 4.36 (1H, d, J=2.8Hz), 4.31 (1H, br t, J=11.4Hz), 3.86 (1H, d, J=14.0Hz), 3.60 (1H, dd, J=11.3Hz), 3.59 (1H, d, J=2.7Hz), 3.53-3.48 (4H, m), 3.35 (1H, d, J=14.1Hz), 3.03 (1H, d, J=11.8Hz), 2.60 (1H, br t,

J=11.9Hz), 2.08-2.00 (2H, m), 1.94-1.84 (2H, m), 1.44 (3H, d, J=6.6Hz).

b) <u>2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(1-(2-pyrrolidinoethyl)-1,2,4-triazol-3-yl)methylmorpholine</u>

Lithium aluminium hydride (1.0M solution in tetrahydrofuran, 1.9ml) was added to a solution of the compound described in (a) above (isomer B) in tetrahydrofuran (5ml) at 0°C. The mixture was warmed to room temperature and was stirred for 1h. The mixture was quenched (sodium hydroxide and water) and filtered through celite to remove inorganics. The filtrate was evaporated and purified on silica using 10% methanol in dichloromethane as eluent. This afforded the product as a yellow oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 8.08 (1H, s), 7.60 (1H, s), 7.49 (2H, br s), 7.37-7.31 (3H, m), 7.13 (2H, s), 4.85 (1H, q, J=6.6Hz), 4.36 (1H, d, J=2.8Hz), 4.33-4.24 (1H, m), 4.22 (2H, t, J=6.5Hz), 3.86 (1H, dd, J=14.1Hz), 3.63 (1H, d, J=9.2Hz), 3.60 (1H, d, J=2.9Hz), 3.38 (1H, dd, J=14.0Hz), 3.00 (1H, d, J=11.7Hz), 2.89 (2H, t, J=6.6Hz), 2.59 (1H, br t, J=11.9Hz), 2.59-2.49 (4H, m), 1.79 (4H, m), 1.43 (3H, d, J=6.5Hz).

<u>EXAMPLE 23</u>

<u>2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(2-pyrrolidinoethyl)-1,2,4-triazol-3-yl)methylmorpholine</u>

The compound described in Example 22a (isomer A) was reacted according to the procedure described in Example 22b to afford the title compound as a yellow oil. ^{1}H NMR (250MHz, $CDCl_3$) δ 7.80 (1H, s, C<u>H</u>), 7.61 (1H, s, Ar<u>H</u>), 7.53-7.48 (2H, m, Ph<u>H</u>), 7.38-7.34 (3H, m), 7.17 (2H, s), 4.88 (1H, q, J=6.5Hz), 4.36 (1H, d, J=2.9Hz), 4.34-4.20 (1H, m), 4.23-4.07 (3H, m), 3.83 (1H, d,

J=14.0Hz), 3.66 (1H, m), 3.42 (1H, d, J=2.8Hz), 3.27 (1H, d, J=14.1Hz), 2.88-2.73 (1H, m), 2.88-2.73 (2H, m), 2.88-2.73 (1H, m), 2.50 (3H, br s), 1.73 (4H, br s), 1.4 (4H, d, J=6.6Hz).

EXAMPLE 24

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-morpholinomethyl-1,2,3-triazol-4-yl) methylmorpholine

This compound was prepared by the method described in Example 12 (Method A) and purified by chromatography on silica using ethyl acetate, petroleum ether (60-80°C) and methanol (3:10:0, then 1:0:0 followed by 9:0:1) as eluent to afford the title compound as a white foam. ^1H NMR (360MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 2.43 (4H, m), 2.57 (1H, dd, J=11.9, 3.4Hz), 2.90 (1H, d, J=11.6Hz), 3.27 (1H, d, J=14.1Hz), 3.46-3.67 (8H, m), 3.82 (1H, d, J=14.1Hz), 4.23 (1H, m), 4.32 (1H, d, J=2.8Hz), 4.87 (1H, m), 7.06 (2H, t, J=8.7Hz), 7.16 (2H, s), 7.48 (2H, br s), 7.64 (1H, s). MS (ES^+) m/z 618 (MH^+, 54%).

Examples 25 to 27 in Table 2 were prepared in a similar manner to that described in Example 12, Method B, via the appropriate N-(4-azidobut-2-ynyl)morpholine and the appropriate amine.

EXAMPLE 28

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(2-chloro-5-morpholinomethyl-1,3-imidazol-4-yl)-3-(S)-(4-fluorophenyl) morpholine

The product from Example 7 (0.2g) and phosphorus oxychloride (0.5ml) was heated at reflux for 20 hours. The mixture was cooled

and partitioned between dichloromethane and aqueous potassium carbonate solution. The organic layer was washed (H_2O), dried ($MgSO_4$) and evaporated *in vacuo*. The product was purified by chromatography on silica using 100% ethyl acetate followed by 5% methanol:95% ethyl acetate to afford the title compound as an oil. MS (ES^+) m/z 651 (MH^+, 100%).

EXAMPLE 29

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl) morpholine

4,5-Bis(chloromethyl)imidazole hydrochloride (British Patent Specification No.GB-2,068,362-A) was reacted with the compound of Description 5 according to the procedure illustrated in Example 4 to afford the title compound as a white solid. ^1H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6Hz), 2.19 (3H, s), 2.46-2.62 (1H, m), 2.92-3.07 (2H, m), 3.25-3.44 (3H, m), 3.56-3.70 (2H, m), 4.16-4.33 (2H, m), 4.85 (1H, q, J=6Hz), 7.01-7.17 (4H, m), 7.38-7.67 (4H, m). MS (ES) m/z 575 ($M+1^+$, 100%).

EXAMPLE 30

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

3,5-Bis(chloromethyl)triazole (*J. Het. Chem.* (1986) 23, 361-368) was reacted with the compound of Description 5 according to the procedure illustrated in Example 4 to afford the title compound as a solid. ^1H NMR (250MHz, $CDCl_3$) δ 1.27 (3H, d, J=6.6Hz), 2.15 (6H, s, CH_3), 2.43 (1H, dt, J=11.7, 3.2Hz), 2.79-2.83 (1H, m), 3.16

(1H, d, J=14.5Hz), 3.38 (1H, d, J=2.8Hz), 3.43-3.48 (1H, m), 3.48 (2H, s, CH_2), 3.63 (1H, d, J=14.5Hz), 4.12 (1H, dt, J=11.7, 3.2Hz), 4.15 (1H, d, J=2.8Hz), 4.69 (1H, q, J=6.6Hz), 6.85 (2H, t, J=8.75Hz), 6.97 (2H, s), 7.27 (2H, br t), 7.45 (1H, s). MS (ES) m/z 576 (M^++1, 100%).

Examples 31 to 37 in Table 2 were prepared in a similar manner to that described in Example 12, Method B, via the appropriate N-(4-azidobut-2-ynyl)morpholine and the appropriate amine.

Examples 38 to 41 in Table 1 were prepared in a similar manner to that described in Example 4 from the appropriate morpholine, 4,5-bis(bromomethyl)-1,3-diacetyl-2-imidazolinone and the appropriate amine.

EXAMPLE 42

2-(R)-(1-(R)-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-thiomorpholinomethyl-1,3-imidazol-4-yl)methylmorpholine S-oxide

The compound of Example 38 (67mg; 1eq) was dissolved in CF_3CO_2H (0.3ml) under N_2 then cooled to 0° C and a solution of CF_3CO_3H (2M in CF_3CO_2H; 57μl; 1.1 eq) was added. After stirring at 0° C for 1h the solvent was removed *in vacuo* and the residue dissolved in EtOAC and washed with saturated aqueous. $NaHCO_3$ solution, dried (K_2CO_3) and concentrated to leave a yellow foam. This was purified by column chromatography using $MeOH/CH_2Cl_2/NH_3$ (3:97:0.25) as eluant to provide the title compound as a white solid. ^1H NMR (250MHz, $CDCl_3$) δ 9.48 (1H, s), 8.66 (1H, s), 7.64 (1H, s), 7.40 (2H, m), 7.14 (2H, s), 7.06 (2H, t,

J=8.6Hz), 4.87 (1H, q, J=6.5Hz), 4.30 (1H, d, J=2.7Hz), 4.23 (1H, t, J=10.0Hz), 3.65 (1H, d, J=9.6Hz), 3.45 (1H, m), 3.75 (1H, m), 3.36 (1H, d, J=2.7Hz), 3.30 (1H, d, J=14Hz), 3.20 (1H, d, J=14Hz), 3.05-2.60 (9H, m), 2.36 (1H, m), 1.46 (3H, d, J=6.5Hz).

Examples 43 to 62 in Table 2 were prepared in a similar manner to that described in Example 12, Method B, via the appropriate N-(4-azidobut-2-ynyl)morpholine and the appropriate amine.

EXAMPLE 63

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(1-(2-(N,N-disopropylamino)ethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-phenylmorpholine

(a) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(1-(2-hydroxyethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-phenylmorpholine

The compound of Description 19 (3.90g, 7.8mM) was heated (60°C) in dimethylformamide (20ml) containing 2-bromoethanol (1.66ml, 23.4mM) and potassium carbonate (3.23g, 23.4mM) for 2 hrs. The reaction was poured into ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated. The two isomers were purified and separated on silica eluting with methanol-dichloromethane mixtures (3.06g). MS (ES^+) m/z 545.

(b) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(1-(2-tosyloxyethyl)-1,2,4-triazol-3-yl)methylmorpholine

The alcohol from step (a), above, (1.81g, 3.22mM) was dissolved in dichloromethane (20ml), tosyl chloride (1.84g, 9.66mM) and triethylamine (1.34ml, 9.66mM) were added and the reaction stirred at room temperature for 18hrs. The solvent was

removed and the residue redissolved in ethyl acetate and washed with water and brine, dried ($MgSO_4$) and evaporated. The product was purified on silica eluting with methanol-dichloromethane mixtures (1.87g).

(c) 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(1-(2-(N,N-disopropylamino)ethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-phenylmorpholine

The tosylate from step (b), above, (0.29g, 0.41mM) was dissolved in dimethylformamide (5ml), dipropylamine (0.18ml, 1.24mM) and triethylamine (0.18ml, 1.24mM) were added and the reaction heated in a sealed tube for 18hrs. The residue was dissolved in ethyl acetate, washed with water and brine, dried ($MgSO_4$) and evaporated. Purification on silica eluting with methanol-dichloromethane mixtures afforded the title compound (0.095g). ^{1}H NMR (360MHz, d_6-DMSO) δ 8.31 (1H, s), 7.82 (1H, s), 7.46-7.42 (2H, m), 7.36 (2H, s), 7.32-7.22 (3H, m), 4.89-4.92 (1H, q, J=6.5Hz), 4.34 (1H, d, J=2.8Hz), 4.18-4.04 (3H, m), 3.60-3.56 (3H, m), 3.09 (1H, d, J=13.6Hz), 3.94 (1H, d, J=11.5Hz), 2.71 (2H, t, J=5.8Hz), 2.44-2.40 (1H, m), 2.30 (4H, t, J=7.0Hz), 1.34 (3H, d, J=6.5Hz), 1.32-1.20 (4H, m) and 0.73 (6H, t, J=7.4Hz). M/S$^+$ 628.

Examples 64 to 74 in Table 3 were prepared in a similar manner to that described in Example 63 from the appropriate 1,2,4-triazol-3-ylmethylmorpholine and the appropriate amine.

EXAMPLE 75

2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

(a) 2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(1-(tetrahydro-2-pyranyl)-5-(N,N-dimethylaminomethyl)-1H-1,2,4-triazol-3-yl)methylmorpholine

The compound of Description 5 (1g, 2.28mM) was dissolved in isopropanol (20ml), 3,5-bis(chloromethyl)-1-(tetrahydro-2-pyranyl)-1H-1,2,4-triazole (1.14g, 4.57mM) (prepared by method of Bradshaw, *J. Het. Chem.* (1986), 23, 361) and potassium carbonate (0.95g, 6.84mM) were added and the reaction heated to 60° C for 18hrs. Dimethylamine (3eq) was then added and the reagents transferred to a sealed tube and heated for a further 18hrs. The solvents were then removed and the residue purified on silica eluting with methanol dichloromethane-ammonia mixtures to yield the title compound (0.62g).

(b) 2-(R)-(1-(R)-3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

The protected amine from step (a), above, (0.62g, 0.94mM) was dissolved in methanol (15ml) and treated with HCl in methanol (1N, 25ml) and stirred at room temperature for 1 hour. The solvent was then removed and the residue purified on silica eluting with methanol-dichloromethane ammonia mixtures to yield the title compound (0.48g). ^{1}H NMR (250MHz,$CDCl_3$) δ 7.45 (1H, s), 7.30-7.22 (2H, m), 6.97 (2H, s), 6.85 (2H, t, J=8.7Hz), 4.72-4.66 (1H, q,

J=6.5Hz), 4.15 (1H, d, J=2.8Hz), 4.15-4.07 (1H, m), 3.63 (1H, d, J=14.4Hz), 3.48 (4H, s), 3.44-3.41 (1H, m), 3.38 (1H, d, J=2.8Hz), 3.16 (1H, d, J=14.5Hz), 2.81 (1H, d, J=11.1Hz), 2.50-2.39 (1H, m), 2.15 (6H, s) and 1.27 (3H, d, J=6.6Hz). M/S ES$^+$ 576.

EXAMPLE 76

4-(5-(N,N-Dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-methylthio-5-(trifluoromethyl)phenyl)ethoxy)morpholine

The compound of Example 57 (270mg, 0.51mmol) was heated to 120°C with sodium thiomethoxide (178mg, 2.55mmol) in anhydrous DMF (10ml) for between 2-5 hours. The cooled solution was diluted with water (150ml), extracted with ethyl acetate (4 x 40ml), dried ($MgSO_4$) and concentrated *in vacuo* to a crude oil (372mg) which was purified by flash silica gel chromatography in 5-10% methanol/dichloromethane to yield the title compound as a viscous gum/glass (170mg, 60%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.31 (3H, d, J=6.6Hz), 2.17 (6H, s), 2.28 (3H, s), 2.47 (1H, dt, J=12.1, 3.4Hz), 2.82 (1H, d, J=11.6Hz), 3.14 (1H, d, J=13.9Hz), 3.35 (2H, m), 3.46 (1H, d, J=13.5Hz), 3.52 (1H, dd, J=11.2, 1.9Hz), 3.70 (1H, d, J=13.9Hz), 4.14 (1H, dt, J=11.6Hz), 4.26 (1H, d, J=2.7Hz), 4.66 (1H, q, J=6.5Hz), 6.64 (2H, s), 6.99 (2H, t, J=8.6Hz), 7.11 (1H, s), 7.41 (2H, br s), 10.0-10.8 (1H, vbr s); MS (ES$^+$) m/z 554 (M+1, 100%).

EXAMPLE 77

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-methylthio-5-(trifluoromethyl)phenyl)ethoxy)-4-(5-pyrrolidinomethyl-1,2,3-triazol-4-yl)methylmorpholine

The title compound was prepared from the compound of Example 18 according to the method of Example 76 as a foam (620mg, 81%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.40 (3H, d, J=6.6Hz), 1.79 (4H, br s), 2.36 (3H, s), 2.5-2.6 (5H, m), 2.87 (1H, d, J=11.7Hz), 3.23 (1H, d, J=13.9Hz), 3.43 (1H, d, J=2.8Hz), 3.57-3.64 (2H, m), 3.71 (1H, d, J=13.7Hz), 3.78 (1H, d, J=14.0Hz), 4.21 (1H, m), 4.33 (1H, d, J=2.8Hz), 4.74 (1H, q, J=6.5Hz), 6.71 (2H, s), 7.06 (2H, t, J=8.7Hz), 7.19 (1H, s), 7.47 (2H, br s); MS (ES^+) m/z 580 (M+1, 100%).

EXAMPLE 78

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-methylthio-5-(trifluoromethyl)phenyl)ethoxy)-4-(5-morpholinomethyl-1,2,3-triazol-4-yl)methylmorpholine

The title compound was prepared from compound of Example 19 according to the method of Example 76 as a foam (126mg, 66%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.40 (3H, s, J=6.6Hz), 2.37 (3H, s), 2.32-2.49 (4H, m), 2.54 (1H, dt, J=11.9, 3.4Hz), 2.90 (1H, d, J=11.7Hz), 3.25 (1H, d, J=13.9Hz), 3.48 (1H, d, J=13.5Hz), 3.57-3.68 (7H, m), 3.82 (1H, d, J=14.1Hz), 4.23 (1H, m), 4.35 (1H, d, J=2.8Hz), 4.75 (1H, q, J=6.5Hz), 6.71 (2H, s), 7.06 (2H, t, J=8.7Hz), 7.19 (1H, s), 7.49 (2H, br s); MS (ES^+) m/z 596 (M+1, 55%), 203 (100%).

EXAMPLE 79

4-(5-(N,N-Dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-2-(R)-(1-(R)-(3-methylthio-5-(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenylmorpholine

The title compound was prepared from the triazole of Example 102 according to the method of Example 76 as a foam (116mg, 36%). ^{1}H NMR (250MHz,$CDCl_3$) δ 1.39 (3H, d, J=6.5Hz), 2.24 (6H, s), 2.32 (3H, s), 2.59 (1H, dt, J=11.8, 3.3Hz), 3.25 (1H, d, J=13.8Hz), 3.38-3.44 (2H, m), 3.52 (1H, d, J=13.6Hz), 3.62 (1H, dd, J=11.2, 1.8Hz), 3.81 (1H, d, J=13.9Hz), 4.23 (1H, m), 4.39 (1H, d, J=2.6Hz), 4.75 (1H, q, J=6.5Hz), 6.71 (2H, s), 7.17 (1H, s), 7.34-7.41 (3H, m), 7.49 (2H, br s); MS (ES$^+$) m/z 536 (M+1, 100%).

EXAMPLE 80

4-(5-(N,N-Dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-*tert*-butylthio-5-(trifluoromethyl)phenyl)ethoxy)morpholine

The title compound was prepared from the compound of Example 57 according to the method of Example 76 as a foam (117mg, 68%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.19 (9H, s), 1.42 (3H, d, J=6.6Hz), 2.23 (6H, s), 2.57 (1H, dt, J=12.0, 3.5Hz), 2.92 (1H, d, J=11.6Hz), 3.24 (1H, d, J=13.9Hz), 3.39-3.44 (2H, m), 3.51 (1H, d, J=14.8Hz), 3.62 (1H, m), 3.80 (1H, d, J=13.9Hz), 4.23 (1H, m), 4.41 (1H, d, J=2.7Hz), 4.77 (1H, q, J=6.5Hz), 6.89 (1H, s), 7.14 (1H, s), 7.31-7.35 (3H, m), 7.46 (2H, br s), 7.51 (1H, s); MS (ES$^+$) m/z 578 (M+1, 100%).

EXAMPLE 81

4-(5-(N,N-Dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-methylsulphinyl-5-(trifluoromethyl)phenyl)ethoxy)morpholine

The thioether of Example 76 (155mg, 0.28mmol) was dissolved in trifluoroacetic acid (800μl) cooled to 0°C and treated with a 2.0M

solution of trifluoroperacetic acid in trifluoroacetic acid (153μl, 0.308mmol), with stirring for 30 minutes. The reaction mixture was poured into 0.5M sodium bicarbonate solution (50ml), extracted with dichloromethane (3 x 15ml), dried ($MgSO_4$) and concentrated *in vacuo*. The resulting crude solid (200mg) was purified by flash silica gel chromatography in 8% methanol : dichloromethane to yield the title compound as unresolved stereoisomers as a white foam (81mg, 51%). ^1H NMR (360MHz,$CDCl_3$) δ 1.44 and 1.46 (3H total, 2 x d, J=6.6Hz), 2.24 (6H, s), 2.56 (1H, m), 2.59 and 2.62 (3H total, 2 x s), 2.88 (1H, d, J=11.9Hz), 3.23 and 3.26 (1H total, 2 x d, J=13.9Hz), 3.42-3.55 (3H, m), 3.62 (1H, br d, J=11.3Hz), 3.75 and 3.79 (1H total , 2 x d, J=14.4Hz), 4.22 (1H, m), 4.32 and 4.35 (1H total, 2 x d, J=2.7Hz), 4.89 (1H, m), 6.85 (½H, s), 7.04-7.13 (3H, m), 7.24 (½H, s), 7.50 (2H, br s), 7.73 and 7.75 (1H total, 2 x s); MS (ES^+) m/z 570 (M+1, 100%).

EXAMPLE 82

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-methylsulphinyl-5-(trifluoromethyl) phenyl)ethoxy)-4-(5-pyrrolidinomethyl-1,2,3-triazol-4-yl)methylmorpholine

The title compound as an unresolved mixture of stereoisomers was prepared from Example 77 according to the method of Example 81 as a foam (90mg, 63%). ^1H NMR (360MHz,$CDCl_3$) δ 1.44 and 1.46 (3H total, 2 x d, J=6.6), 1.86 (4H, br s), 2.50-2.60 (1H, m), 2.59 and 2.62 (3H total, 2 x s), 2.70-2.90 (5H, m), 3.24 and 3.26 (1H, 2 x d, J=14.0), 3.46 (1H, d, J<2), 3.62 (1H, br d, J=11.2), 3.71-3.86 (3H, m), 4.20 (1H, m), 4.32 and 4.35 (1H total, 2 x d, J=2.7), 4.89 (1H, m), 6.89 (½H, s), 7.03-7.13 (3H, m), 7.25 (½H, s), 7.49 (2H, br s), 7.73 and 7.75 (1H total, 2 x s); MS (ES^+) m/z 596 (M+1), 100%).

EXAMPLE 83

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-methylsulphinyl-5-(trifluoromethyl) phenyl)ethoxy)-4-(5-morpholinomethyl-1,2,3-triazol-4-yl)methylmorpholine

The title compound as an unresolved mixture of stereoisomers was prepared from Example 78 according to the method of Example 81 as a foam (113mg, 92%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.3 and 1.41 (3H total, 2 x d, J=6.6), 2.54 and 2.57 (3H total, 2 x s), 2.54-2.65 (1H, m), 2.82-2.89 (1H, m), 3.05-3.25 (4H, vbr s), 3.35 (1H, m), 3.50 (1H, m), 3.61 (1H, m), 3.72 and 3.74 (1H, 2 x d, J=14.5), 3.85-4.22 (6H, m), 4.29 and 4.33 (1H, 2 x d, J=2.5), 4.81 (1H, m), 6.99-7.09 (3½H, m), 7.30 (½H, s), 7.42 (2H, br s), 7.64 and 7.66 (1H total, 2 x s); MS (ES$^+$) m/z 612 (M+1, 100%).

EXAMPLE 84

3-(S)-(4-Fluorophenyl)-2-(R)-(1-(R)-(3-methylsulphonyl-5-(trifluoromethyl) phenyl)ethoxy)-4-(5-morpholinomethyl-1,2,3-triazol-4-yl)methylmorpholine

The sulphoxide of Example 83 (78mg, 0.128mmol) was dissolved in trifluoroacetic acid (500μl) cooled to 0°C and treated with a 2.0M solution of trifluoroperacetic acid in trifluoroacetic acid (70μl, 0.140mmol) with stirring for 2½ hours. A further equivalent of trifluoroperacetic acid (70μl, 0.140mmol) was added after this time and the product purified after 3 hours according to the method of Example 81 to yield the title compound as a foam (27mg, 34%). ^{1}H NMR (360MHz,$CDCl_3$) δ 1.47 (3H, d, J=6.6Hz), 2.38-2.45 (4H, m), 2.57 (1H, dt, J=11.9, 3.5), 2.90 (1H, d, J=11.7Hz), 2.96 (3H, s), 3.26 (1H, d, J=14.0Hz), 3.46-3.51 (2H, m), 3.56-3.68 (6H, m), 3.79 (1H,

d, J=14.1Hz), 4.22 (1H, m), 4.35 (1H, d, J=2.8Hz), 4.90 (1H, q, J=6.8Hz), 7.07 (2H, t, J=8.6Hz), 7.17 (1H, s), 7.50 (2H, br d), 7.67 (1H, s), 7.97 (1H, s); MS (ES^+) m/z 628 (M+1, 100%).

EXAMPLE 85

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2-(5-((S)-(+)-2-methoxymethylpyrrolidinomethyl)-1,2,3-triazol-4-yl)ethyl)morpholine

Step A 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(but-3-ynyl)-3-(S)-(4-fluorophenyl)morpholine

A solution of Description 5 (1.24g; 1eq), 3-butyn-1-ol-tosylate (1.43g; 2.5 eq), K_2CO_3 (1.32g; 3.7 eq) and NaI (cat) in dry DMF (7ml) was heated at 100°C for 12h. After cooling to room temperature the reaction mixture was partitioned between H_2O and EtOAc. The layers were separated and the aqueous phase extracted with EtOAc (2x). The combined organic phases were dried ($MgSO_4$) and concentrated and the residue purified by chromatography (hexanes/EtOAc 9:1→4:1) to provide the title compound as a clear cololourless oil. MS m/z 490 (MH^+).

Step B 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(4-hydroxybut-3-ynyl)morpholine

The acetylene of Step A (1.2g; 1.0eq) was dissolved in dry THF (5ml) then cooled to -78°C and n-BuLi (2.5M in hexane; 1ml; 1.05eq) was added. The reaction mixture was stirred at -78°C for 1h, then HCHO gas was bubbled through the solution until it was saturated. The reaction mixture was warmed to room temperature and stirred for 1h. Work-up (NH_4Cl/EtOAc) followed by purification

on silica gel (hexanes/EtOAc 9:1→4:1) provided the title compound as a clear, viscous oil. MS m/z 520 (MH^+).

Step C 2-((R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(4-chlorobut-3-ynyl)-3-(S)-(4-fluorophenyl)morpholine

The alcohol of Step B (0.42g; 1eq) was dissolved in dry THF (5ml) under N_2 and triphosgene (84mg; 0.35 eq) was added followed by pyridine (128 μl; 2.0 eq). The reaction mixture was stirred at room temperature for ½h, then diluted with EtOAc and washed with H_2O and brine, dried ($MgSO_4$) and concentrated to leave a yellow oil. This was purified by chromatography (hexanes/EtOAc 9:1→4:1) to provide the title compound as a clear, viscous oil. MS m/z 538, 540 (MH^+).

Step D N-(4-Azidobut-3-ynyl)-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine

The chloride of Step C (0.23g; 1eq) and NaN_3 (31mg; 1eq) in DMSO (0.8ml) was stirred at room temperature for 14h. Work-up (NH_4Cl/EtOAc) provided the title compound as an oil, which was used without further purification.

Step E 2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2-(5-((S)-(+)-2-methoxymethylpyrrolidinomethyl)-1,2,3-triazol-4-yl)ethyl)morpholine

A solution of the azide of Step D (0.205g; 1 eq) and (S)-(+)-2-methoxymethylpyrrolidine (114μl; 3 eq) was heated at 80°C under N_2 the solvent was removed *in vacuo* and the residue purified by chromatography using CH_2Cl_2/MeOH/NH_3 (98:2:0.1 then 97:3:0.1) as eluant to provide the title compound as a white foam. ^1H NMR

(250MHz, $CDCl_3$) δ 7.62 (1H, s), 7.24 (2H, m), 7.14 (2H, s), 6.95 (2H, t, J=8.7Hz), 4.87 (1H, q, J=6.5Hz), 4.30 (2H, m), 3.95 (1H, d, J=14Hz), 3.70 (1H, dd, J=2, 11.3Hz), 3.53-3.34 (7H, m), 3.19 (1H, d, J=11.6Hz), 2.86-2.56 (6H, m), 2.29 (1H, m), 2.09 (1H, m), 1.88 (1H, m), 1.70 (3H, m), 1.45 (3H, d, J=6.5Hz). MS m/z=660.

EXAMPLE 86

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

Step A 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-*tert*-butyldimethylsilyloxyethoxy)-3-(S)-(4-fluorophenyl)morpholine

The product from Description 21 (2g) was dissolved in anhydrous dichloromethane (16ml), under nitrogen, and cooled to 0°C. 2,6-Lutidine (0.5ml) and *tert*-butyldimethyltrifluoromethane sulfonate (1.0ml) were then added and the mixture stirred for 15 mins. The reaction mixture was washed (H_2O, brine), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by gravity silica column using 20%-50% ethylacetate/petrol as eluant afforded the title compound as a colourless oil.

^{1}H NMR (250MHz, $CDCl_3$) δ -0.04 (3H, s), 0.00 (3H, s), 0.87 (9H, s), 3.15-3.36 (2H, m), 3.64-3.70 (2H, m), 3.90-3.96 (1H, m), 4.10 (1H, d, J=2.2Hz), 4.22-4.53 (1H, m), 4.53 (1H, d, J=2.2Hz), 4.91 (1H, t, J=5.9Hz), 7.04-7.14 (2H, m), 7.29-7.36 (4H, m), 7.74 (1H, br s). MS (ES^+) m/z=567.

Step B 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-*tert*-butyldimethylsilyloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(4-chlorobut-2-ynyl)morpholine

Prepared in an analogous fashion to Step (a) of Example 12, Method B, using the product from Step A, above, to afford the title compound as a clear oil. ^{1}H NMR (360MHz, $CDCl_3$) δ 0.00 (3H, s), 0.04 (3H, s), 0.91 (9H, s), 2.95-3.09 (2H, m), 3.40 (2H, br s), 3.72-3.83 (3H, m), 4.01 (1H, dd, J=10.2, J=5.5Hz), 4.25 (2H, m), 4.50 (2H, m), 4.9 (1H, t, J=5.9Hz), 7.15 (2H, t, J=8.7Hz), 7.29 (2H, s), 7.52 (2H, br s), 7.76 (1H, s).

Step C 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-*tert*-butyldimethylsilyloxyethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

Prepared in an analogous fashion to Steps (b) and (c) of Example 12, Method B, using the product of Step B, above, to afford the title compound. ^{1}H NMR (250MHz, $CDCl_3$) δ -0.02 (3H, s), 0.00 (3H, s), 0.88 (9H, s), 2.30 (6H, s), 2.60-2.70 (1H, m), 2.93-2.98 (1H, br d, J=11.6Hz), 3.30 (1H, d, J=13.8Hz), 3.48-3.63 (3H, m), 3.68-3.74 (2H, m), 3.84-3.97 (2H, m), 4.33-4.41 (1H, m), 4.46 (1H, d, J=2.8Hz), 4.90 (1H, t, J=5.6Hz), 7.16 (2H, t, J=8.7Hz), 7.25 (2H, br s), 7.59 (2H, vbr m), 7.74(1H, br s).

Step D 2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine

The product of Step C, above, (0.2g) was stirred in anhydrous tetrahydrofuran (2ml) with tetrabutylammonium fluoride (1.0M) in tetrahydrofuran (0.42ml) for 30 minutes. The mixture was

partitioned between ammonium chloride solution and ethylacetate, and the organic layer washed (H_2O, brine), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by gravity silica column eluting with 4-10% MeOH/0.1% NH_4OH/dichloromethane afforded the title compound. ^{1}H NMR (250MHz, $CDCl_3$) δ 2.26 (6H, s), 2.51 (1H, m), 3.09 (2H, m), 3.35 (2H, m), 3.51-3.63 (4H, m), 3.78 (2H, d, J=13.8Hz), 4.30-4.36 (2H, m), 4.88 (1H, m), 7.01-7.10 (4H, m), 7.50 (2H, vbr s), 7.59 (1H, br s).

EXAMPLE 87

2-(R)-(1-(R)-(3,5-Bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N-ethyl-N-isopropylaminomethyl)-1(or 2 or 3)-methyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine

The product from Example 101 (2g) was dissolved in N,N-dimethylformamide (4ml) at room temperature under nitrogen. Iodomethane was added, followed by sodium hydride (60%) (14mg) and the mixture stirred for 16 hours. The reaction mixture was partitioned between ethylacetate and water and the organic layer was washed (H_2O x 2, brine), dried ($MgSO_4$) and evaporated *in vacuo*. Purification by gravity silica chromatography eluting with 100% ethylacetate followed by 10% methanol/0.1% NH_4OH/dichloromethane afforded the title compound.

^{1}H NMR (250MHz, $CDCl_3$) δ 0.85-1.02 (9H, m), 1.44 (3H, d, J=6.6Hz), 2.25-2.40 (2H, m), 2.57-2.68 (1H, m), 2.75-2.85 (1H, m), 2.96 (1H, br d, J=13.5Hz), 3.15 (1H, d, J=13.5Hz), 3.38 (1H, d, J=2.7Hz), 3.44 (2H, s), 3.60-3.73 (2H, m), 4.07 (3H, s), 4.18 (1H, m), 4.35 (1H, d, J=2.8Hz), 4.83 (1H, m), 7.15 (2H, br s), 7.33 (3H, m), 7.48 (2H, vbr s), 7.61 (1H, br s). MS (ES^+) m/z=613 (MH^+, 100%).

EXAMPLE 88

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine

The compound of Description 6 (0.5g), N-carbomethoxy-2-chloroacetamidrazone (Description 23) (182mg) and potassium carbonate (0.3g) were suspended in dimethylformamide (3.6ml) and the mixture was heated to 60°C for 2h. The mixture was then heated to 140°C for a further 2h. The mixture was cooled and the inorganic material was removed by filtration through celite. The solvent was removed *in vacuo* by azeotroping with xylene. The residue was purified on silica by flash chromatography using 1-10% methanol in dichloromethane. This afforded the title compound as a white powder (300mg). ^{1}H NMR (360MHz, DMSO-d_6) δ 2.38-2.41 (1H, m), 2.78 (1H, d, J=14.0Hz), 2.81-2.84 (1H, m), 3.36 (1H, d, J=14.0Hz), 3.45-3.48 (1H, m), 3.52 (1H, d, J=3.0Hz), 3.58-3.61 (2H, m), 4.81 (1H, t, J=6.0Hz), 4.88 (1H, br t), 7.09 (2H, t, J=9.0Hz), 7.33 (2H, s), 7.50 (2H, br t), 7.85 (1H, s), 11.26 (1H, s), 11.30 (1H, s). MS (CI$^+$) m/z 551 (M$^+$1, 10%), 454 (M$^+$-CH$_2$triazolone, 20).

EXAMPLE 89

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine

The compound of Description 6 (270mg), anhydrous potassium carbonate (250mg), and N-formyl-2-chloroacetamidhydrazone (92mg) (prepared according to I. Yanagisawa, *J. Med. Chem.* (1984), 27, 849) were heated at 60°C in anhydrous dimethylformamide for 1h and then at 140°C for 2h. The reaction

mixture was cooled and diluted with water (100ml). The product was extracted into ethyl acetate (3 x 50ml) and the organic layer was washed with brine, dried ($MgSO_4$) and evaporated *in vacuo*. The residue was purified by chromatography on silica using 7% methanol in dichloromethane as the eluant. This afforded the title compound (200mg, 60%) as a white solid. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.47 (1H, t, J=9.0Hz), 2.89 (1H, d, J=11.0Hz), 3.18 (1H, d, J=14.0Hz), 3.44-3.49 (1H, m), 3.55-3.61 (4H, m), 3.64 (1H, d, J=6Hz), 4.25 (1H, t, J=11.0Hz), 4.34 (1H, d, J=3.0Hz), 4.81 (1H, t, J=5.0Hz), 7.11 (2H, t, J=9.0Hz), 7.34 (2H, s), 7.52 (2H, m), 7.85 (1H, s), 8.19 (1H, br s). MS (CI) m/z 535 (M+1, 10%).

EXAMPLE 90

4-(2,3-Dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

The compound of Description 22 (350mg), N-carbomethoxy-2-chloroacetamidrazone (150mg) (Description 23) and potassium carbonate (150mg) in dimethylformamide were heated at 60°C for 3h until all starting material was consumed. The mixture was then heated at 140°C for 3h. The mixture was cooled and filtered through celite to remove inorganics. The residue was evaporated using xylene to azeotrope residual dimethylformamide. The residue was purified by chromatography on silica using 1-10% methanol in dichloromethane as eluant. This afforded the title compound as a foam which was recrystallised from ether. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.34-2.46 (1H, m), 2.74-2.84 (2H, m), 3.34-3.43 (3H, m), 3.50-3.60 (2H, m), 4.21-4.31 (2H, m), 4.68 (1H, t, J=5.0Hz),

4.90 (1H, t, J=7.0Hz), 6.54 (1H, d, J=9.0Hz), 6.88 (1H, s), 7.14 (t, J=9.0Hz), 7.42 (1H, d, J=9.0Hz), 7.44 (2H, m).

EXAMPLE 91

4-(2,3-Dihydro-2-oxo-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl) morpholine

A mixture of the compound of Description 6 (2g), 4-bromomethyl-1,3-diacetyl-2-imidazolone (1.38g) (prepared by the method of Dolan and Dushinsky, *JACS* (1948) 70, 657) and potassium carbonate (1.2g) in dimethylformamide (14ml) was stirred at room temperature for 30 minutes until all starting morpholine had reacted. The mixture was diluted with water (150ml) and extracted with ethyl acetate (3 x 50ml). The combined extracts were washed with brine and the organic solvent was evaporated *in vacuo*. The residual oil was dissolved in ethanol (20ml) and methylamine (2ml of 8M soln. in ethanol) was added. This solution was stirred for 1h and the solvent was then removed *in vacuo*. The residual oil was purified on silica using 1-10% methanol in dichloromethane as eluant. This afforded the product (2g, 83%) as a white foam. This was further characterised by treatment with methanolic hydrogen chloride to afford a white solid which was recrystallised from water. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.22-2.34 (1H, m), 2.62 (1H, d, J=14.0Hz), 2.89 (1H, app d, J=11.0Hz), 3.26 (1H, d, J=14.0Hz), 3.38 (1H, d, J=3.0Hz), 3.43-3.50 (1H, m), 3.57-3.62 (2H, m), 4.19-4.28 (1H, m), 4.32 (1H, d, J=3.0Hz), 4.81 (1H, t, J=5.5Hz), 4.93 (1H, t, J=6.0Hz), 6.00 (1H, s), 7.09 (1H, t, J=9.0Hz), 7.33 (2H, s), 7.54 (2H, br t), 7.86 (1H, s), 9.63 (1H, s), 9.83 (1H, s). MS (CI) m/z 550 (M+1, 20%), 454 (80) 116 (100).

EXAMPLE 92

4-(2,3-Dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)morpholine

A mixture of the compound of Description 6 (1.8g), 4,5-bis(bromomethyl)-1,3-diacetyl-2-imidazolone (prepared by the method of Dolan and Dushinsky, *JACS* (1948) 70, 657) (2.2g) and potassium carbonate in dimethylformamide (13ml) were stirred at room temperature for 10 min until all starting material was reacted. To the resulting brown mixture was added dropwise pyrrolidine (1.65ml, excess) resulting in an exothermic reaction. The solvent was removed *in vacuo* and the residue was extracted with ethyl acetate (3 x 50ml) and washed with brine. The organic phase was dried ($MgSO_4$) and the solvent removed *in vacuo*. The brown residue was purified by medium pressure reverse phase C_{18} silica gel chromatography using 30% acetonitrile in 0.1% aqueous trifluoroacetic acid as eluant. This afforded the title product as a buff coloured solid (1g). ^{1}H NMR (360MHz, DMSO-d_6) δ 1.61 (4H, br s), 2.26-2.30 (5H, m), 2.66 (1H, d, J=14.0Hz), 2.83-2.87 (1H, brd), 3.02 (1H, d, J=13.5Hz), 3.15 (1H, d, J=13.5Hz), 3.23 (1H, d, J=14.0Hz), 3.37 (1H, d, J=3.0Hz), 3.42-3.47 (1H, m), 3.57-3.60 (2H, m), 4.17-4.24 (1H, m), 4.32 (1H, d, J=3.0Hz), 4.79 (1H, t, J=5.5Hz), 4.89 (1H, t, J=5.5Hz), 7.08 (2H, t, J=9.0Hz), 7.32 (2H, s), 7.56 (2H, mc), 7.85 (1H, s), 9.61 (1H, s), 9.65 (1H, s). MS (CI^+) m/z 633 (M^++1), 454 (50%).

EXAMPLE 93

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine

The compound of Example 88 (200mg) in dry tetrahydrofuran (1ml) was treated with dibenzyloxydiethylaminophosphine (200mg) and tetrazole (100mg). The reaction was stirred for 2 hours and then treated with a further 100mg of dibenzyloxydiethyl aminophosphine followed after 1 hour by tetrazole (100mg). The reaction was stirred for a further 1 hour before adding 4-methylmorpholine-N-oxide (1.0g) and stirring for 16 hours. The reaction was poured into potassium carbonate solution and extracted into ethyl acetate. The organic layer was dried ($MgSO_4$), filtered, evaporated and purified by chromatography on silica gel using methanol/dichloromethane (4:96) as eluent to yield an oil. This was dissolved in methanol (2ml) and ammonium formate (100mg) and palladium hydroxide (20% on carbon) was added. The reaction mixture was heated to reflux for one hour and then filtered, evaporated and freeze dried from acetonitrile/water to give the ammonium salt of the title compound (93mg); ^{1}H NMR (360MHz, D_6-DMSO) δ 11.29 (1H, s), 7.85 (1H, s), 7.53 (2H, s), 7.36 (2H, m), 7.06 (2H, t, J=7.2Hz), 4.96 (1H, t, J=5.4Hz), 4.34 (1H, d, J=3.6Hz), 4.29 (1H, t, J=11.2Hz), 3.92-3.85 (1H, m), 3.68-3.63 (1H, m), 3.62-3.55 (1H, m), 3.49 (1H, d, J=3.6Hz), 3.38 (1H, d, J=14.4Hz), 2.82-2.79 (1H, m), 2.77 (1H, d, J=14.4Hz), 2.41-2.35 (1H, m); MS (ES^+) 631 (M+H.

EXAMPLE 94

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl) methylmorpholine

The ammonium salt of the title compound was prepared from the compound of Example 89 by the methodology of Example 93. ^{1}H NMR (250MHz, D_6-DMSO + 0.1% TFA) δ 8.74 (1H, s), 7.95 (1H, s), 7.68 (2H, broad s), 7.54 (2H, s), 7.30 (2H, t, J=8.7Hz), 5.16 (1H, dd, J=7Hz and 5Hz), 4.72 (1H, d, J=1Hz), 4.66 (1H, d, J=1Hz), 4.42 (1H, t, J=11Hz), 3.95-4.27 (3H, m), 3.72 (1H, d, J=11Hz) and 3.41-3.55 (1H, m).

EXAMPLE 95

4-(2,3-Dihydro-3-oxo-1,2,4-triazol-5-yl)-3-(S)-phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

Prepared from the compound of Description 30 following the method illustrated in Example 88. MS (CI$^+$) m/z 465 ((M+1)$^+$, 71%).

EXAMPLE 96

4-(2,3-Dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine

The compound of Description 27 (600mg), N-carbomethoxy-2-chloroacetamidrazone (271mg) and potassium carbonate (258mg) were reacted in dimethylformamide according to the procedure illustrated in Example 88. This afforded the product as a white solid which was recrystallised from ether/hexane (220mg, 30%). ^{1}H NMR (360MHz, DMSO-d_6) δ 2.38 (1H, m), 2.78 (1H, d, J=14.0Hz), 2.84 (1H, s), 3.38-3.39 (2H, m), 3.45 (1H, d, J=14.0Hz), 3.50 (1H, d, J=3.0Hz), 3.56 (1H, d, J=11.0Hz), 4.26 (1H, t, J=11.0Hz), 4.34 (1H,

d, J=3.0Hz), 4.68 (1H, t, J=6.0Hz), 4.85 (1H, t, J=6.0Hz), 6.40 (1H, d, J=9.0Hz), 6.96 (1H, s), 7.33 (3H, m), 7.36 (1H, d, J=9.0Hz), 7.49 (2H, m). MS (CI^+) m/z 483 (M+1, 20%).

EXAMPLE 97

4-(2,3-Dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-3-fluoro-5-(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-phenylmorpholine

The ammonium salt of the title compound was prepared from the compound of Example 96 using the methodology of Example 93. ^{1}H NMR (360MHz, DMSO-d_6) δ 11.29 (1H, s), 7.49-7.29 (5H, m), 7.38 (1H, d, J=10.8Hz), 6.96 (1H, s), 6.45 (1H, d, J=10.8Hz), 4.84 (1H, d, J=7.2Hz), 4.34 (1H, d, J=3.6Hz), 4.28 (1H, t, J=10.8Hz), 3.80-3.76 (1H, m), 3.57 (1H, d, J=3.6Hz), 3.57-3.49 (2H, m), 3.47 (1H, d, J=14.4Hz), 2.83-2.76 (1H, m), 2.78 (1H, d, J=14.4Hz), 2.46-2.36 (1H. m).

EXAMPLE 98

2-(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-phenylmorpholine

The compound of Description 17 was reacted with N-carbomethoxy-2-chloroacetamidrazone (Description 23) and potassium carbonate according to the procedure illustrated in Example 88. This afforded the product as a white solid. ^{1}H NMR (360MHz, DMSO-d_6) δ 2.42 (1H, dt, J=12.0, 3.5Hz), 2.76 (1H, d, J=14.0Hz), 2.83 (1H, d, J=12.0Hz), 3.39 (1H, d, J=14.0Hz), 3.44-3.47 (1H, m), 3.50 (1H, d, J=3.0Hz), 3.60 (2H, m), 4.22-4.28 (1H, m), 4.40 (1H, d, J=3.0Hz), 4.77-4.83 (2H, m), 7.25-7.34 (3H, m),

7.41 (2H, s), 7.48-7.50 (2H, m), 7.82 (1H, s), 11.20 (1H, s), 11.25 (1H, s), MS (CI) m/z 533 (M+1, 30%) 434 (20), 117 (100).

EXAMPLE 99

2(R)-(1-(S)-(3,5-Bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-phenylmorpholine

The ammonium salt of the title compound was prepared from Example 98 by the method of Example 93. ^{1}H NMR (360MHz, d_6-DMSO) δ 11.26 (1H, s), 7.83 (1H, s), 7.48-7.24 (7H, m), 4.95 (1H, t, J=5.4), 4.39 (1H, d, J=3.6), 4.29 (1H, t, J=11.2), 3.92-3.89 (1H, m), 3.60-3.64 (1H, m), 3.55-3.59 (1H, m), 3.48 (1H, d, J=3.6), 3.42 (1H, d, J=14.4), 2.84-2.79 (1H, m), 2.78 (1H, d, J=14.4), 2.42 (1H, m). HPLC on Zorbax Z-Ph (250 x 4.6mm i.d. 5μM) column eluting with 40% acetonitrile in 25mM KH_2PO_4 with 0.2% triethylamine (pH 3.0), flow rate 1ml/min, UV detector 210nM. Retention time 4.68 min.

EXAMPLE 100

3-(S)-Phenyl-4-(1,2,4-triazol-3-yl)-2-(R)-(1-(S)-3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine

Prepared as a hydrochloride salt from the compound of Description 30 following the method illustrated in Example 89. MS (ES$^+$) m/z 449 ((M+1)$^+$ 100%).

Examples 101 and 102 in Table 2 were prepared in a similar manner to that described in Example 12, Method B, via the appropriate N-(4-azidobut-2-ynyl)morpholine and the appropriate amine.

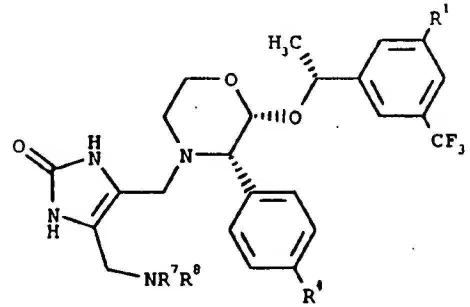


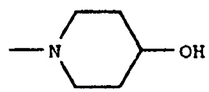
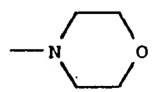
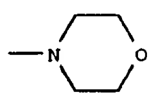
TABLE 1				
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
5	CF_3	F		MS (CI^+) m/z 635 (M^++H). Anal. Calcd. for $C_{30}H_{31}F_7N_4O_2$: C, 54.89; H, 5.24; N, 8.38. Found: C, 54.63; H, 5.32; N, 8.38%.
6	F	F		^{1}H NMR (250MHz, $CDCl_3$) δ 8.31 (1H, br s), 8.17 (1H, br s), 7.37 (2H, br m), 7.04-7.11 (3H, m), 6.77 (1H, s), 6.33 (1H, d, J=9.0Hz), 4.75 (1H, m), 4.17-4.30 (2H, m), 3.58-3.69 (5H, m), 3.44 (1H, d, J=14.0Hz), 3.38 (1H, d, J=3.0Hz), 3.13 (2H, dd, J=19.91, 14.0Hz), 2.91 (1H, d, J=11.5Hz), 2.75 (1H, d, J=14.01Hz), 2.34 (5H, m), 1.41 (3H, d, J=6.5Hz). MS (CI^+) m/z 583.
7	CF_3	F		^{1}H NMR (360MHz, DMSO) δ 9.71 (1H, s), 9.65 (1H, s), 7.85 (1H, s), 7.55 (2H, br s), 7.37 (2H, s), 7.07 (2H, t, J=8.85Hz), 4.91 (1H, m), 4.31 (1H, d, J=2.83Hz), 4.07 (1H, m), 3.61 (1H, br d, J=10.76Hz), 3.51 (4H, m), 3.36 (1H, d, J=2.70Hz), 3.27 (1H, d, J=10.34Hz), 3.08 (1H, d, J=13.6Hz), 2.93 (1H, d, J=13.6Hz), 2.86 (1H, d, J=11.51Hz), 2.61 (1H, d, J=13.6Hz), 2.27 (5H, m), 1.35 (3H, d, J=6.55Hz). MS (CI^+) m/z = 633.

TABLE 1 (continued)

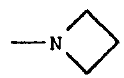
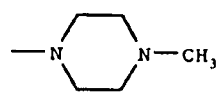
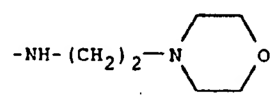
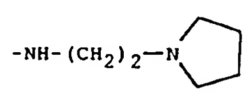
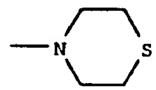
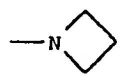
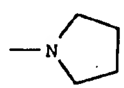
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
8	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 9.16 (1H, br s), 8.14 (1H, br s), 7.64 (1H, s), 7.38 (2H, br s), 7.09 (4H, m), 4.86 (1H, m), 4.22 (2H, m), 3.64 (1H, d, J=9.34Hz), 3.38 (2H, m), 3.16 (6H, m), 2.93 (1H, d, J=11.28Hz), 2.75 (1H, d, J=11.3Hz), 2.36 (1H, m), 2.05 (2H, m), 1.45 (3H, d, J=6.59Hz). MS (CI^+) m/z 603.
9	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 8.03 (1H, s), 8.00 (1H, s), 7.63 (1H, s), 7.38 (2H, m), 7.06 (4H, m), 4.86 (1H, m), 4.28 (1H, d, J=2.8Hz), 4.19 (1H, d, J=11.47Hz), 3.64 (1H, d, J=9.41Hz), 3.38 (2H, m), 3.13 (2H, dd, J=13.61, 17.28Hz), 2.92 (1H, d, J=11.5Hz), 2.73 (1H, d, J=11.5Hz), 2.28-2.40 (12H, m), 1.45 (3H, d, J=6.6Hz). MS (CI^+) m/z 646
10	CF_3	F		^{1}H NMR (250MHz, DMSO) δ 10.52 (½H, s), 9.87 (½H, s), 9.80 (½H, s), 9.66 (½H, s), 8.32 (1H, s), 7.86 (1H, s), 7.53 (2H, br s), 7.37 (2H, br s), 7.09 (2H, m), 4.93 (1H, m), 4.32 (1H, d, J=2.76Hz), 4.02 (2H, m), 3.62 (1H, d, J=11.78Hz), 3.52 (5H, m), 3.26 (2H, m), 2.86 (1H, m), 2.59 (1H, m), 2.31 (6H, m), 1.97 (3H, d, J=7.37Hz), 1.36 (3H, d, J=6.24Hz). MS (CI^+) m/z 676
11	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 7.63 (1H, s), 7.39 (2H, br s), 7.12 (2H, s), 7.04 (2H, m), 4.86 (1H, m), 4.28 (1H, d, J=2.7Hz), 4.18 (1H, m), 4.10 (1H, s), 3.67 (1H, s), 3.60 (1H, m), 3.39 (2H, m), 2.36-2.92 (10H, m), 2.07 (1H, s), 1.95 (4H, m), 1.45 (3H, d, J=6.53Hz).

TABLE 1 (continued)

Ex. No.	R^1	R^4	$-NR^7R^8$	Data
38	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 9.35 (1H, s), 8.94 (1H, s), 7.78 (1H, s), 7.71 (2H, br m), 7.13 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.4Hz), 4.30 (1H, d, J=2.8Hz), 4.24 (1H, m), 3.64 (1H, d, J=9.6Hz), 3.43 (1H, d, J=14Hz), 3.37 (1H, d, J=2.8Hz), 3.20 (1H, d, J=14Hz), 3.10 (1H, d, J=14Hz), 2.95 (1H, d, J=11.3Hz), 2.75 (1H, d, J=14Hz), 2. 62 (8H, s), 2.35 (1H, m), 1.49 (3H, d, J=6.4Hz). MS m/z 647 (MH^+).
39	F	F		^{1}H NMR (250MHz, $CDCl_3$) δ 10.06 (1H, s), 8.85 (1H, s), 7.40 (2H, br s), 7.08 (3H, t, J=8.7Hz), 6.77 (1H, s), 6.33 (1H, d, J=8.7Hz), 4.75 (1H, q, J=6.4Hz), 4.29 (1H, d, J=2.8Hz), 4.22 (1H, m), 3.62 (1H, d, J=9.8Hz), 3.49 (1H, d, J=14Hz), 3.38 (1H, d, J=2.8Hz), 3.16 (5H, m), 2.96 (1H, d, J=11.4Hz), 2.81 (1H, d, J=14Hz), 2.40 (1H, m), 2.05 (2H, m), 1.40 (3H, d, J=6.4Hz). MS m/z 553 (MH^+).
40	F	F	$-N(CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.41 (3H, d, J=6.6Hz), 2.20 (6H, s), 2.34 (1H, m), 2.75 (1H, d, J=14.1Hz), 2.92 (1H, d, J=11.4Hz), 3.09 (2H, m), 3.37 (1H, d, J=2.8Hz), 3.44 (1H, d, J=14.1Hz), 3.62 (1H, m), 4.22-4.29 (2H, m), 4.75 (1H, m), 6.33 (1H, d, J=9.0Hz), 6.77 (1H, s), 7.08 (3H, m), 7.37 (2H, br s), 8.18 (1H, s), 8.92 (1H, s). MS (ES^+) m/z 540.
41	F	F		^{1}H NMR (360MHz, $CDCl_3$) δ 7.36 (2H, br s), 7.07 (3H, t, J=8.5Hz), 6.77 (1H, s), 6.33 (1H, d, J=8.5Hz), 4.76 (1H, q, J=6.4Hz), 4.28 (1H, d, J=2.7Hz), 4.22 (1H, m), 3.62 (1H, d, J=9.8Hz), 3.49 (1H, d, J=14Hz), 3.37 (1H, d, J=2.8Hz), 3.28 (2H, s), 2.91 (1H, d, J=7.9Hz), 2.75 (1H, d, J=9.7Hz), 2.45 (4H, m), 2.33 (1H, m), 1.74 (4H, m), 1.41 (3H, d, J=6.4Hz).

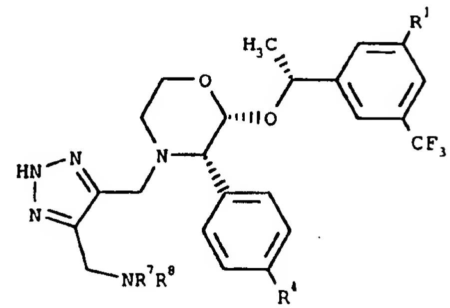


TABLE 2

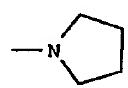
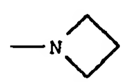
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
14	CF_3	F	$-NHCH_3$	HRMS (EI^+) (found M^+, 561.1975. $C_{25}H_{26}F_7N_5O_2$ requires M^+, 561.1975). Analysis Calcd. for $C_{25}H_{26}F_7N_5O_2.0.5H_2O$: C, 52.54; H, 4.94; N, 12.25; Found: C, 52.67; H, 4.64; N, 12.08%.
15	CF_3	F	$-NH_2$	MS m/z (CI^+) 548 (M+H).
16	CF_3	F		Analysis Calcd. for $C_{28}H_{30}F_7N_5O_2$: C, 55.90; H, 5.03; N, 11.64; Found: C, 55.71; H, 4.86; N, 11.53%. MS m/z (CI^+) 602 (M+H).
17	F	F		^1H NMR (360MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.6), 2.13 (2H, qn, J=7.1), 2.55 (2H, dt, J=12.0, 3.4), 2.88 (1H, d, J=11.7), 3.22-3.45 (5H, m), 3.57-3.66 (4H, m), 3.80 (1H, d, J=14.0), 4.20 (1H, dt, J=11.6, 2.1), 4.32 (1H, d, J=2.9), 4.76 (1H, q, 6.5), 6.39 (1H, d, J=8.9), 6.80 (1H, s), 7.05-7.12 (3H, m), 7.48 (2H, br s). MS (CI^+) m/z 538 (M+1, 100%).

TABLE 2 (continued)

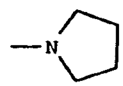
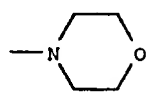
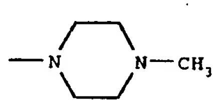
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
18	F	F		^{1}H NMR (360MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.6), 1.81 (4H, br s), 2.53-2.61 (5H, m), 2.89 (1H, d, J=11.7), 3.27 (1H, d, J=14.0), 3.45 (1H, d, J=2.8), 2.59-3.63 (1H, m), 3.63 (1H, d, J=13.7), 3.73 (1H, d, J=13.7), 3.83 (1H, d, J=14.0), 4.21 (1H, dt, J=11.6, 2.1), 4.32 (1H, d, J=2.8), 4.76 (1H, q, J=6.5), 6.37 (1H, d, J=9.1), 6.80 (1H, s), 7.05-7.10 (3H, m), 7.46 (2H, br s). MS (CI^+) 552 (M+1, 100%).
19	F	F		^{1}H NMR (360MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.6), 2.4-2.5 (4H, m), 2.56 (1H, dt, J=11.9, 3.4), 2.90 (1H, d, J=11.6), 3.30 (1H, d, J=14.1), 3.48-3.52 (2H, m), 3.58-3.71 (6H, m), 3.85 (1H, d, J=14.2), 4.23 (1H, dt, J=11.6, 2.3), 4.33 (1H, d, J=2.8), 4.77 (1H, q, J=6.5), 6.37 (1H, d, J=8.8), 6.80 (1H, s), 7.05-7.10 (3H, m), 7.46 (2H, br s). MS (CI^+) m/z 568 (M+1, 100%).
20	H	F	$-N(CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.5), 2.25 (6H, s), 2.55 (1H, dt, J=11.8, 3.4), 2.91 (1H, d, J=11.6), 3.23 (1H, d, J=13.9), 3.41-3.64 (4H, m), 3.80 (1H, d, J=13.9), 4.24 (1H, t, J=11.5), 4.33 (1H, d, J=2.7), 4.77 (1H, q, J=6.5), 6.80 (1H, d, J=7.7), 6.95 (1H, s), 7.06 (2H, t, J=8.7), 7.16 (1H, t, J=7.7), 7.36 (1H, d, J=7.8), 7.48 (2H, br s), 9.3-9.9 (1H, br s). MS (CI^+) 508 (M+1, 100%).
21	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 7.63 (1H, s), 7.48 (2H, br s), 7.15 (2H, s), 7.05 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.6Hz), 4.30 (1H, d, J=2.7Hz), 4.21 (1H, br t, J=11.4Hz), 3.77 (1H, d, J=13.9Hz), 3.67 (1H, d, J=14.0Hz), 3.65 (1H, m), 3.56 (1H, d, J=14.0Hz), 3.43 (1H, d, J=2.7Hz), 3.20 (1H, d, J=13.9Hz), 2.85 (1H, d, J=11.5Hz), 2.56-2.48 (9H, m), 2.31 (3H, s), 1.42 (3H, d, J=6.6Hz).

TABLE 2 (continued)

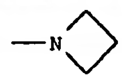
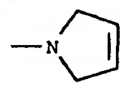
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
25	CF_3	F		^{1}H NMR (360MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 2.14 (2H, m), 2.55 (1H, dd, J=3.4, 11.9Hz), 2.87 (1H, d, J=11.9Hz), 3.21-3.44 (6H, m), 3.58-3.67 (3H, m), 3.75 (1H, d, J=14.0Hz), 4.2 (1H, t, J=9.3Hz), 4.31 (1H, d, J=2.8Hz), 4.85 (1H, m), .06 (2H, t, J=8.7Hz), 7.16 (1H, s), 7.47 (2H, br s), 7.63 (1H, s).
26	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, J=6.7Hz), 2.57 (1H, dd, J=3.4, 11.9Hz), 2.90 (1H, d, J=11.6Hz), 3.23 (1H, d, J=3.9Hz), 3.45-3.66 (6H, m), 3.75-3.84 (3H, m), 4.08-4.26 (1H, m), 4.31 (1H, d, J=2.8Hz), 4.86 (1H, m), 5.78 (2H, s), 7.05 (2H, t, J=8.7Hz), 7.15 (2H, s), 7.47 (2H, brt), 7.64 (1H, s).
27	CF_3	F	$-N(CH_2CH_2OCH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.58Hz), 2.73 (5H, m), 2.95 (1H, d, J=11.8Hz), 3.23 (1H, d, J=13.9Hz), 3.37 (6H, s), 3.41-3.49 (5H, m), 3.63-3.86 (4H, m), 4.18 (1H, t, J=11.5Hz), 4.30 (1H, d, J=2.8Hz), 4.84 (1H, m), 7.06 (2H, t, J=8.7Hz), 7.14 (2H, s), 7.45 (2H, br t), 7.63 (1H, s). MS (ES^+) m/z 664 (MH^+, 100%).
31	CF_3	H	$-N(CH_3)CH_2CH(OCH_3)_2$	1H NMR (250MHz, $CDCl_3$) δ 1.43 (3H, d, J=6.5Hz), 2.17 (3H, s), 2.53 (2H, d, J=5.0Hz), 2.60-2.73 (1H, br dt), 2.95 (1H, br d), 3.30 (3H, s), 3.32 (3H, s), 3.31 (1H, d, J=14.0Hz), 3.44 (1H, d, J=2.7Hz), 3.56 (1H, d, J=2.0Hz), 3.64 (1H, br d), 3.82 (1H, d, J=14.0Hz), 4.20-4.29 (1H, br t), 4.36 (1H, d, J=2.7Hz), 4.47 (1H, t, J=5.0Hz), 4.85 (1H, q, J=6.5Hz), 7.14 (2H, s), 7.27-7.38 (3H,m), 7.45 (2H, br s), 7.61 (1H, s). MS (ES) m/z 632 (M++1, 100%)

TABLE 2 (continued)

Ex. No.	R^1	R^4	$-NR^7R^8$	Data
32	CF_3	H	$-NH(CH_2)_2OCH_3$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.45 (3H, d, J=6.5Hz), 2.50 (1H, dt, J=3.4, 12.0Hz), 2.79-2.87 (3H, m), 3.16 (1H, d, J=14.0Hz), 3.35 (3H, s), 3.41 (1H, d, J=2.7Hz), 3.51-3.67 (3H, m), 3.75-3.87 (3H, m), 4.24 (1H, br t), 4.36 (1H, d, J=2.7Hz), 4.87 (1H, q, J=6.5Hz), 7.16 (2H, s), 7.33-7.39 (3H, m), 7.46 (2H, m), 7.61 (1H, s). MS (ES) m/z 588 (M^++1, 100%).
33	CF_3	H	$-N(CH_3)(CH_2)_2OCH_3$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.43 (3H, d, J=6.5Hz), 2.24 (3H, s), 2.58 (2H, t, J=3.5Hz), 2.65 (1H, br t), 2.94 (1H, br d), 3.29 (1H, d, J=9.5Hz), 3.36 (3H, s), 3.43 (1H, d, J=2.0Hz), 3.49 (2H, t, J=3.5Hz), 3.56 (2H, s), 3.63 (1H, dd, J=1.3, 7.75Hz), 3.80 (1H, d, J=9.5Hz), 4.23 (1H, dt, J=1.5, 8.0Hz), 4.36 (1H, d, J=2.0Hz), 4.84 (1H, q, J=6.5Hz), 7.15 (2H, s), 7.32-7.36 (3H, m), 7.45 (2H, m), 7.61 (1H, s). MS (ES) m/z 602 (M^++1, 100%).
34	CF_3	H	$-N[CH(CH_3)_2](CH_2)_2OCH_3$	^{1}H NMR (250MHz, $CDCl_3$) δ 0.99 (3H, d, J=6.5Hz), 1.02 (3H, d, J=6.5Hz), 1.43 (3H, d, J=6.5Hz), 2.64-2.71 (3H, m), 2.91-2.98 (2H, m), 3.26(1H, d, J=14.0Hz), 3.39 (6H, s), 3.43 (1H, d, J=2.6Hz), 3.49-3.81 (3H, m), 4.22 (1H, dt, J=2.0, 11.5Hz), 4.35 (1H, d, J=2.6Hz), 4.86 (1H, q, J=6.5Hz), 7.14 (2H, s), 7.31-7.35 (3H, m), 7.45 (2H, m), 7.61 (1H, s). MS (ES) m/z 630 (M^++1, 100%).

TABLE 2 (continued)

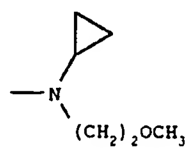
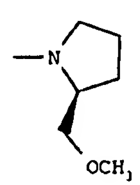
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
35	CF_3	H		^{1}H NMR (250MHz, $CDCl_3$) δ 0.29-0.42 (4H, m), 1.43 (3H, d, J=6.5Hz), 1.63 (1H, br qn), 2.72 (2H, t, J=5.0Hz), 2.7-2.74 (1H, m), 3.02-3.07 (1H, m), 3.27-3.37 (1H, m), 3.37 (3H, s), 3.43 (1H, d, J=2.8Hz), 3.55 (2H, t, J=5.0Hz), 3.62-3.70 (3H, m), 3.82 (1H, d, J=14.0Hz), 4.25 (1H, br t), 4.34 (1H, d, J=2.8Hz), 4.84 (1H, q, J=6.5Hz), 7.13 (2H, s), 7.33-7.36 (3H, m), 7.43 (2H, m), 7.61 (1H, s). MS (ES) m/z 628 (M^++1, 100%).
36	CF_3	H	$-N(CH_2CH_2CH_2CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 0.85 (6H, t, J=7.25Hz), 1.14-1.38 (9H, m), 1.44 (3H, d, J=6.5Hz), 2.34 (4H, br t), 2.63-2.73 (2H, m), 2.97 (1H, m), 3.34 (1H, d, J=14.0Hz), 3.41-3.47 (3H, m), 3.64 (1H, dd, J=2.0, 11.0Hz), 3.79 (1H, d, J=14.0Hz), 4.26 (1H, br t), 4.35 (1H, d, J=2.8Hz), 4.84 (1H, q, J=6.5Hz), 7.14 (2H, s), 7.32-7.35 (3H, m), 7.43 (2H, m), 7.61 (1H, s).
37	CF_3	H	$-N[CH(CH_3)_2]_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.01 (12H, d, J=7.25Hz), 1.43 (3H, d, J=6.5Hz), 2.68 (1H, dt, J=3.5, 12.5Hz), 2.92-3.02 (3H, m), 3.32 (1H, d, J=14.0Hz), 3.44 (1H, d, J=2.8Hz), 3.48 (1H, br d), 3.52-3.72 (2H, m), 3.77 (1H, d, J=14.0Hz), 4.24 (1H, br t), 4.36 (1H, d, J=2.8Hz), 4.85 (1H, q, J=6.5Hz), 7.14 (2H, s), 7.32-7.35 (3H, m), 7.45 (2H, m), 7.61 (1H, s).
43	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 1.52-1.92 (4H, m), 2.26 (1H, m), 2.61-2.77 (2H, m), 2.93 (2H, m), 3.26 (2H, d, J=14.0Hz), 3.36 (5H, m), 3.61-3.89 (4H, m), 4.23 (1H, m), 4.30 (1H, d, J=2.8Hz), 4.86 (1H, m), 7.06 (2H, t, J=8.8Hz), 7.15 (2H, s), 7.46 (2H, br s), 7.63 (1H, s). MS (ES^+) m/z 645.

TABLE 2 (continued)

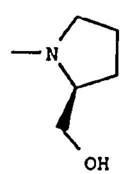
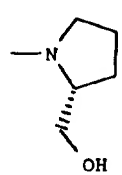
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
44	CF_3	F	$-N[CH(CH_3)_2]_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.30 (6H, d, J=6.5Hz), 1.31 (6H, d, J=6.5Hz), 1.75 (3H, d, J=6.6Hz), 2.95 (1H, m), 3.20-3.31 (3H, m), 3.57 (1H, d, J=14.1Hz), 3.78 (2H, m), 3.92-4.05 (3H, m), 4.53 (1H, m), 4.62 (1H, d, J=2.80Hz), 5.17 (1H, m), 7.35 (2H, t, J=8.7Hz), 7.46 (2H, s), 7.76 (2H, m), 7.94 (1H, s). MS (ES^+) m/z 631.
45	CF_3	F	$-N(CH_2CH_2CH_3)CH_2CH_2OH$	^{1}H NMR (250MHz, $CDCl_3$) δ 7.64 (1H, s), 7.49 (2H, br s), 7.17 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.5Hz), 4.31 (1H, d, J=2.7Hz), 4.26 (1H, t, J=9.6Hz), 3.74 (1H, d, J=13.7Hz), 3.60 (5H, m), 3.44 (1H, d , J=2.7Hz), 3.15 (1H, d, J=13.7Hz), 2.96 (1H, d, J=11.7Hz), 2.68-2.49 (5H, m), 1.56-1.42 (5H, m), 0.87 (3H, t, J=7.3Hz). MS m/z 634 (MH^+).
46	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 7.63 (1H, s), 7.57 (2H, br s), 7.15 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.5Hz), 4.30 (2H, m), 3.82 (2H, m), 3.64 (2H, d, J=13.5Hz), 3.44 (1H, d, J=2.6Hz), 3.32 (2H, m), 3.15-3.03 (3H, m), 2.88 (1H, m), 2.66-2.47 (2H, m), 1.87 (1H, m), 1.81-1.64 (3H, m), 1.43 (3H, d, J=6.5Hz). MS m/z 632 (MH^+).
47	CF_3	F		^{1}H NMR (250MHz, $CDCl_3$) δ 7.63 (1H, s), 7.57 (2H, br s), 7.15 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.5Hz), 4.32 (1H, d, J=2.7Hz), 4.22 (1H, m), 3.88 (1H, d, J=14.1Hz), 3.74 (1H, d, J=14.0Hz), 3.64-3.54 (3H, m), 3.44 (2H, m), 3.20 (1H, d, J=14Hz), 3.00-2.81 (3H, m), 2.55 (1H, m), 2.34 (1H, m), 1.92 (1H, m), 1.71 (3H, m), 1.44 (3H, d, J=6.5Hz). MS m/z 632 (MH^+).

TABLE 2 (continued)

Ex. No.	R^1	R^4	$-NR^7R^8$	Data
48	CF_3	F	$-N[CH(CH_3)_2]CH_2CH_2OH$	^{1}H NMR (250MHz, $CDCl_3$) δ 7.64 (1H, s), 7.49 (2H, br s), 7.27 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.86 (1H, q, J=6.5Hz), 4.31 (1H, d, J=2.7Hz), 4.14 (1H, m), 3.76-3.43 (7H, m), 3.17 (1H, d, J=13.8Hz), 3.04-2.89 (2H, m), 2.75-2.53 (3H, m), 1.43 (3H, d, J=6.5Hz), 1.5 (6H, d, J=6.6Hz). M/S m/z 634 (MH^+).
49	CF_3	F	$-N(CH_3)C(CH_3)_3$	^{1}H NMR (250MHz, $CDCl_3$) δ 7.63 (1H, s), 7.45 (2H, br s), 7.15 (2H, s), 7.05 (2H, t, J=8.74Hz), 4.87 (1H, q, J=6.58Hz), 4.31 (1H, d, J=2.79Hz), 4.23 (1H, m), 3.75 (1H, d, J=14.16Hz), 3.64 (1H, m), 3.54 (1H, d, J=14.40Hz), 3.48 (1H, d, J=14.40Hz), 3.46 (1H, d, J=2.79Hz), 3.32 (1H, d, J=14.16Hz), 2.94 (1H, d, J=11.73Hz), 2.65 (1H, td, J=10.33, 3.51Hz), 2.09 (3H, s), 1.45 (3H, d, J=6.58Hz), 1.15 (9H, s). M/S (ES^+) 618.
50	CF_3	F	2,5-dimethylpyrrolidino	MS (ES^+) m/z 629 (MH^+, 100%)
51	CF_3	F	$-N(CH_2CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.00 (6H, t, J=7.2Hz), 1.44 (3H, d, J=6.6Hz), 2.46-2.55 (4H, m), 2.62 (1H, m), 2.91 (1H, d, J=11.7Hz), 3.27 (1H, d, J=14.0Hz), 3.46 (1H, d, J=2.7Hz), 3.56 (2H, s), 3.62 (1H, m), 3.77 (1H, d, J=14.1Hz), 4.24 (1H, m), 4.31 (1H, d, J=2.8Hz), 4.86 (1H, m), 7.05 (2H, t, J=8.7Hz), 7.15 (2H, s), 7.47 (2H, br s), 7.64 (1H, s). MS (ES^+) m/z 603
52	CF_3	H	$-N(CH_3)_2$	Analysis Calcd. for $C_{26}H_{29}N_5O_2F_6.HCl.H_20$: C, 51.03; H, 5.27; N, 11.44. Found C, 51.21; H, 5.24; N, 11.10%. M.pt. 127-129°C.

TABLE 2 (continued)

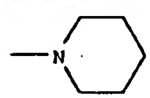
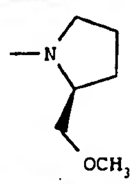
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
53	CF_3	H	$-N(CH_2CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 1.03 (6H, t, J=7.1Hz), 1.44 (3H, d, J=6.6Hz), 2.51-2.70 (5H, m), 2.93 (1H, d, J=11.6Hz), 3.32 (1H, d, J=14.1Hz), 3.44 (1H, d, J=2.7Hz), 3.57-3.66 (3H, m), 3.80 (1H, d, J=14.1Hz), 4.24 (1H, m), 4.35 (1H, d, J=2.7Hz), 4.85 (1H, m), 7.14 (2H, s), 7.27 (1H, s), 7.34 (3H, m), 7.45 (2H, br s), 7.61 (1H, s). MS (ES$^+$) m/z 585.
54	CF_3	H	$-N(CH_2CH_2CH_3)_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 0.82 (6H, t, J=7.4Hz), 1.35-1.46 (7H, m), 2.36 (4H, m), 2.66 (1H, m), 2.95 (1H, d, J=11.6Hz), 3.35 (1H, d, J=14.2Hz), 3.44 (1H, d, J=2.78Hz), 3.53 (2H, s), 3.64 (1H, m), 3.78 (1H, d, J=14.3Hz), 4.26 (1H, m), 4.35 (1H, d, J=2.8Hz), 4.85 (1H, m), 7.14 (2H, s), 7.33 (3H, m), 7.43 (2H, br s), 7.61 (1H, s). MS (ES$^+$) m/z 613.
55	CF_3	H		^{1}H NMR (250MHz, $CDCl_3$) δ 1.44-1.56 (9H, m), 2.35 (4H, m), 2.61 (1H, m), 2.92 (1H, d, J=11.7Hz), 3.29 (1H, d, J=14.0Hz), 3.40-3.56 (3H, m), 3.83 (1H, d, J=14.0Hz), 4.24 (1H, m), 4.36 (1H, d, J=2.8Hz), 4.86 (1H, m), 7.15 (2H, s), 7.34 (3H, m), 7.47 (2H, br s), 7.61 (1H, s). MS (ES$^+$) m/z 597.
56	CF_3	H		^{1}H NMR (250MHz, $CDCl_3$) δ 1.44 (3H, d, J=6.6Hz), 1.52-1.91 (4H, m), 2.28 (1H, m), 2.66-2.75 (2H, m), 2.93 (2H, m), 3.28-3.43 (7H, m), 3.62 (2H, m), 3.80 (2H, d, J=14.2Hz), 4.22 (1H, m), 4.35 (1H, d, J=2.7Hz), 4.85 (1H, m), 7.14 (2H, s), 7.33 (3H, m), 7.44 (2H, br s), 7.61 (1H, s). MS (ES$^+$) m/z 627.

TABLE 2 (continued)

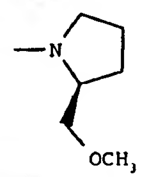
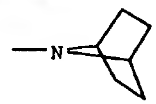
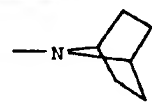
Ex. No.	R^1	R^4	$-NR^7R^8$	Data
57	F	F	$-N(CH_3)_2$	^{1}H NMR (360MHz, $CDCl_3$) δ 1.40 (3H, d, J=6.5Hz), 2.24 (6H, s), 2.57 (1H, m), 2.89 (1H, d, J=11.8Hz), 3.27 (1H, d, J=14.0Hz), 3.46 (2H, s), 3.52-3.63 (2H, m), 3.82 (1H, d, J=14.1), 4.22 (1H, t, J=10.4Hz), 4.76 (1H, m), 6.37 (1H, d, J=8.9Hz), 6.80 (1H, s), 7.05-7.10 (3H, m), 7.46 (2H, br s).
58	F	F	$-N(CH_2CH_3)_2$	^{1}H NMR (360MHz, $CDCl_3$) δ 1.01 (6H, t, J=7.1Hz), 1.39 (3H, d, J=6.6Hz), 2.48-2.63 (5H, m), 2.91 (1H, d, J=11.8Hz), 3.30 (1H, d, J=14.1Hz), 3.46 (1H, d, J=2.8Hz), 3.57 (2H, s), 3.60-3.63 (1H, m), 3.81 (1H, d, J=14.1Hz), 4.20-4.26 (1H, m), 4.32 (1H, d, J=2.8Hz), 4.76 (1H, m), 6.36 (1H, d, J=8.9Hz), 6.80 (1H, s), 7.04-7.09 (3H, m), 7.46 (2H, br s).
59				^{1}H NMR (250MHz, $CDCl_3$) δ 7.44 (2H, br s), 7.37 (3H, t, J=3.28Hz), 7.03 (1H, d, J=8.27Hz), 6.81 (1H, s), 6.23 (1H, d, J=9.32Hz), 4.76 (1H, q, J=6.57Hz), 4.34 (1H, d, J=2.80Hz), 4.22 (1H, m), 3.87-3.59 (4H, m), 3.43-3.32 (8H, m), 2.94 (2H, m), 2.72 (2H, m), 2.29 (2H, q, J=8.54Hz), 1.92-1.53 (4H, m), 1.39 (3H, d, J=6.59Hz).
60			$-N[CH(CH_3)_2]_2$	^{1}H NMR (250MHz, $CDCl_3$) δ 7.45 (2H, br s), 7.37 (3H, t, J=2.99Hz), 7.03 (1H, d, J=8.29Hz), 6.82 (1H, s), 6.23 (1H, d, J=9.08Hz), 4.76 (1H, q, J=6.55Hz), 4.35 (1H, d, J=2.83Hz), 4.24 (1H, td, J=1.60Hz, 2.31Hz), 3.82 (1H, d, J=14.20Hz), 3.68 (1H, d, J=13.92Hz), 3.63 (1H, m), 3.50 (1H, d, J=13.92Hz), 3.46 (1H, m), 3.36 (1H, d, J=14.20Hz), 2.97 (3H, m), 2.68 (1H, td, J=12.01Hz, 3.47Hz), 1.39 (3H, d, J=6.55Hz). MS m/z (ES^+) 564.

TABLE 2 (continued)

Ex. No.	R^1	R^4	$-NR^7R^8$	Data
61				^{1}H NMR (250MHz, $CDCl_3$) δ 7.42 (2H, br s), 7.36 (3H, t, J=3.01Hz), 7.03 (1H, d, J=8.29Hz), 6.81 (1H, s), 6.23 (1H, d, J=9.11Hz), 4.76 (1H, q, J=6.62Hz), 4.33 (1H, d, J=2.79Hz), 4.22 (1H, m), 3.85 (1H, d, J=14.06Hz), 3.62 (1H, m), 3.52 (2H, d, J=2.09Hz), 2.65 (1H, td, J=10.34Hz, 3.54Hz), 1.79 (4H, br m), 1.37 (8H, m). MS m/z (ES^+) 560.
62				^{1}H NMR (250MHz, $CDCl_3$) δ 7.61 (1H, s), 7.42 (2H, br s), 7.32 (3H, m), 7.13 (2H, s), 4.84 (1H, q, J=6.5Hz), 4.34 (1H, d, J=2.8Hz), 4.23 (1H, m), 3.81 (1H, d, J=14Hz), 3.63 (1H, dd, J=2.0, 11.2Hz), 3.48 (2H, s), 3.40 (1H, d, J=2.8Hz), 3.25 (1H, d, J=14Hz), 3.22 (2H, t, J=4.2Hz), 2.96 (1H, d, J=11.7Hz), 2.64 (1H, m), 1.76 (4H, m), 1.43 (3H, d, J=6.5Hz), 1.35 (4H, m). MS m/z 610 (MH^+).
101	CF_3	F	$-N[CH(CH_3)_2]CH_2CH_3$	^{1}H NMR (250MHz,$CDCl_3$) δ 0.87-0.95 (9H, m), 1.36 (3H, d, J=6.6Hz), 2.36-2.44 (2H, m), 2.61 (1H, dt, J=12.0Hz, 3.5Hz), 2.83-2.91 (2H, m), 3.28 (1H, d, J=14.1Hz), 3.37-3.45 (3H, m), 3.57 (1H, m), 3.72 (1H, d, J=14.1Hz), 4.17 (1H, dt, J=11.7Hz, 2.4Hz), 4.29 (1H, d, J=2.8Hz), 4.78 (1H, q, J=6.6Hz), 7.07 (2H, s), 7.24-7.29 (3H, m), 7.37 (2H, vbr s), 7.54 (1H, s). MS (ES^+) m/z 599 (MH^+, 100%).
102	F	H	$-N(CH_3)_2$	^{1}H NMR (360MHz,$CDCl_3$) δ 1.39 (3H, d, J=6.6Hz), 2.25 (6H, s), 2.60 (1H, dt, J=11.9, 3.5Hz), 2.91 (1H, d, J=11.5Hz), 3.31 (1H, d, J=14.0Hz), 3.41-3.63 (4H, m), 3.87 (1H, d, J=14.0Hz), 4.23 (1H, br t, J=11.6Hz), 4.35 (1H, d, J=2.8Hz), 4.76 (1H, q, J=6.5Hz), 6.27 (1H, d, J=9.2Hz), 6.83 (1H, s), 7.03 (1H, d, J=8.3Hz), 7.34-7.40 (4H, m), 7.47 (2H, br s). MS (ES^+) m/z 508 (M+1, 100%).

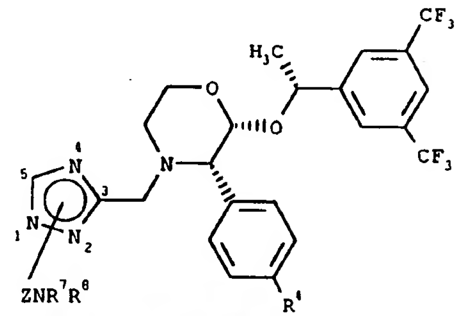


TABLE 3

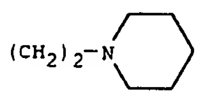
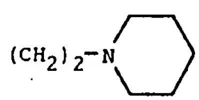
Ex. No.	R^4	$-ZNR^7R^8$	Data
64	H	2 - 	^{1}H NMR (360MHz, d_6-DMSO) δ 7.80 (2H, s), 7.54-7.48 (2H, m), 7.42 (2H, s), 7.36-7.28 (3H, m), 4.92-4.98 (1H, q, J=6.5Hz), 4.38 (1H, d, J=2.7Hz), 4.18-4.00 (3H, m), 3.70 (1H, d, J=14.0), 3.61 (1H, d, J=9.9Hz), 3.54 (1H, d, J=2.7Hz), 3.17 (1H, d, J=14.0Hz), 3.80-3.70 (1H, m), 2.58-2.50 (2H, m), 2.20-2.16 (4H, m), 1.37 (3H, d, J=6.5Hz), 1.32-1.28 (6H, m). M/S$^+$ 612.
65	H	1 - 	^{1}H NMR (360MHz, DMSO) δ 8.35 (1H, s), 7.82 (1H, s), 7.46-7.40 (2H, m), 7.36 (2H, s), 7.32-7.22 (3H, m), 4.89-4.93 (1H, (1H, q, J=6.5), 4.34 (1H, d, J=2.8), 4.19 (2H, t, J=6.2), 4.09 (1H, t, J=11.2), 3.60-3.52 (3H, m), 3.09 (1H, d, J=13.6), 2.93 (1H, d, J=11.7), 2.61 (2H, t, J=6.4), 2.50-2.38 (1H,m), 2.36-2.32 (4H, m), 1.44-1.40 (6H, m), 1.34 (3H, d, J=6.5). M/S+1 612.
66	H	2 - $(CH_2)_2$-$N(CH_2CH_2CH_3)_2$	^{1}H NMR (360MHz, d_6-DMSO) δ 7.84 (1H, s), 7.83 (1H, s), 7.45-7.49 (2H, m), 7.42 (2H, s), 7.32-7.31 (3H, m), 4.92-4.98 (1H, q, J=6.5Hz), 4.38 (1H, d, J=2.7Hz), 4.07-4.11 (1H, m), 3.88-3.95 (2H, m), 3.68 (1H, d, J=14.2Hz), 3.61 (1H, d, J=11.4Hz), 3.53 (1H, d, J=2.7Hz), 3.20 (1H, d, J=14.2Hz), 2.80 (1H, d, J=11.4Hz), 2.65-2.49 (3H, s), 2.17 (4H, t, J=7.1Hz), 1.37 (3H, d, J=6.5Hz), 1.18-1.12 (4H, m), 0.67 (6H, t, J=7.2Hz). MS$^+$ 628.

TABLE 3 (continued)

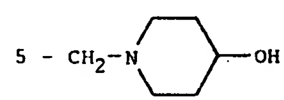
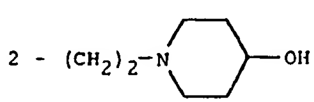
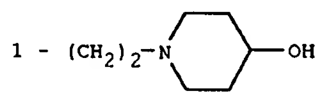
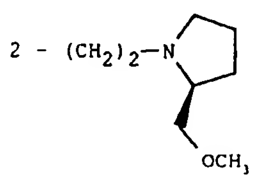
Ex. No.	R^4	$-ZNR^7R^8$	Data
67	H	5 - CH_2-$N(CH_2CH_2CH_3)_2$	^1H NMR (250MHz,$CDCl_3$) δ 7.61 (1H, s), 7.48-7.40 (2H, m), 7.38-7.30 (3H, m), 7.13 (2H, s), 4.88-4.83 (1H, q, J=6.5Hz), 4.36 (1H, d, J=2.8Hz), 4.30 (1H, t, J=11.5Hz), 3.83 (1H, d, J=14.5Hz), 3.65-3.62 (1H, d, J=11.2Hz), 3.55 (1H, d, J=2.7Hz), 3.53 (1H, d, J=14.4Hz), 3.00 (1H, d, J=11.6Hz), 2.66-2.57 (1H, dxt, J=3.5 and 11.9Hz), 2.43 (4H, t, J=7.42Hz), 1.54-1.40 (9H, m), 0.87 (6H, t, J=7.3Hz). M/S ES^+ 614.
68	H	1 - CH_2CH_2-$N(CH_3)_2$	^1H NMR (250MHz,$CDCl_3$) δ 8.01 (1H, s), 7.53 (1H, s), 7.41-7.35 (2H, m), 7.29-7.19 (3H, m), 7.06 (2H, s), 4.79-4.75 (1H, q, J=6.5Hz), 4.29 (1H, d, J=2.80Hz), 4.29-4.19 (1H, m), 4.10 (2H, t, J=6.4Hz), 3.76 (1H, d, J=14.1Hz), 3.57-3.52 (2H, m), 3.26 (1H, d, J=14.1Hz), 2.92 (1H, d, J=11.8Hz), 2.63 (2H, t, J=6.3Hz), 2.52 (1H, dt, J=3.5 and 11.9Hz), 2.18 (6H, s), 1.36 (3H, d, J=6.6Hz). M/S ES^+ 572.
69	F		^1H NMR (250MHz,$CDCl_3$) δ 7.34 (1H, s), 7.18-7.08 (2H, m), 6.85 (2H, s), 6.74 (2H, t, J=8.7Hz), 4.60-4.55 (1H, q, J=6.4Hz), 4.03 (1H, d, J=2.8Hz), 4.04-3.94 (1H, m), 3.48 (1H, d, J=14.8Hz), 3.50-3.34 (4H, m), 3.26 (1H, d, J=2.8Hz), 3.03 (1H, d, J=14.7Hz), 2.66 (1H, d, J=11.7Hz), 2.58-2.42 (2H, m), 2.31 (1H, dt, J=3.4 and 11.9Hz), 2.08-1.94 (2H, m), 1.64-1.54 (2H, m), 1.40-1.24 (2H, m), 1.17 (3H, d, J=6.6Hz). M/S ES^+ 614.
70	H		^1H NMR (250MHz,$CDCl_3$) δ 7.80 (1H, s), 7.61 (1H, s), 7.58-7.42 (2H, m), 7.40-7.36 (3H, m), 7.15 (2H, s), 4.90-4.85 (1H, q, J=6.5Hz), 4.36 (1H, d, J=2.8Hz), 4.27-3.95 (3H, m), 3.82 (1H, d, J=14.0Hz), 3.64-3.60 (2H, m), 3.40 (1H, d, J=2.8Hz), 3.24 (1H, d, J=14.0Hz), 2.89 (1H, d, J=11.9Hz), 2.72-2.61 (5H, m), 2.09 (2H, t, J=9.5Hz), 1.80-1.62 (3H, m), 1.44 (3H, d, J=6.6Hz), 1.43-1.35 (2H, m). M/S ES^+ 628.

TABLE 3 (continued)

Ex. No.	R^4	$-ZNR^7R^8$	Data
71	H		^{1}H NMR (250MHz,$CDCl_3$) δ 8.11 (1H, s), 7.60 (1H, s), 7.50-7.44 (2H, m), 7.38-7.30 (3H, m), 7.13 (2H, s), 4.86-4.81 (1H, q, J=6.5Hz), 4.40-4.14 (4H, m), 3.83 (1H, d, J=14.2Hz), 3.78-3.60 (4H, m), 3.36 (1H, d, J=13.9Hz), 3.98 (1H, d, J=11.8Hz), 2.84-2.52 (5H, m), 2.34-2.18 (1H, m), 1.96-1.44 (5H, m), 1.44 (3H, d, J=6.5Hz). M/S ES^+ 628.
72	F	2 - CH_2CH_2-$N(CH_3)_2$	^{1}H NMR (250MHz,$CDCl_3$) δ 7.80 (1H, s), 7.63 (1H, s), 7.52-7.42 (2H, m), 7.18 (2H, s), 7.07 (2H, t, J=8.7Hz), 4.91-4.86 (1H, q), 4.32 (1H, d, J=2.8Hz), 4.24-4.06 (3H, m), 3.76 (1H, d, J=14.0Hz), 3.64-3.60 (1H, m), 3.44 (1H, d, J=2.8Hz), 3.24 (1H, d, J=13.9Hz), 2.82-2.60 (4H, m), 2.25 (6H, s), 1.62-1.56 (6H, m), 1.46 (3H, d, J=6.6Hz). M/S ES^+ 660.
73	F	1 - CH_2CH_2-$N(CH_3)_2$	^{1}H NMR (250MHz,$CDCl_3$) δ 8.07 (1H, s), 7.62 (1H, s), 7.50-7.40 (2H, m), 7.15 (2H, s), 7.03 (2H, t, J=8.8Hz), 4.87-4.83 (1H, q, J=6.6Hz), 4.35-4.25 (2H, m), 4.17 (2H, t, J=6.4Hz), 3.77 (1H, d, J=14.1Hz), 3.62-3.58 (2H, m), 3.34 (1H, d, J=14.1Hz), 3.00 (1H, d, J=11.6Hz), 2.70 (2H, t, J=6.4Hz), 2.66-2.52 (2H, m), 2.25 (6H, s), 1.43 (3H, d, J=6.6Hz). M/S ES^+ 590.
74	F		^{1}H NMR (360MHz,$CDCl_3$) δ 7.81 (1H, s), 7.63 (1H, s), 7.52-7.42 (2H, m), 7.16 (2H, s), 7.06 (2H, t, J=8.7Hz), 4.90-4.86 (1H, q, J=6.6Hz), 4.32 (1H, d, J=2.8Hz), 4.24 (1H, m), 4.10-4.02 (2H, m), 3.74 (1H, d, J=14.0Hz), 3.62-3.58 (1H, m), 3.46 (1H, d, J=2.8Hz), 3.30-3.28 (5H, m), 3.06-3.02 (2H, m), 2.88 (1H, m), 2.80-2.58 (4H, m), 2.22-2.18 (1H, m), 1.82-1.78 (1H, m), 1.70-1.58 (4H, m), 1.46 (3H, d, J=6.6Hz). M/S ES^+ 590.

The following examples illustrate pharmaceutical compositions according to the invention.

EXAMPLE 103A Tablets containing 1-25mg of compound

	Amount mg		
Compound of formula (I)	1.0	2.0	25.0
Microcrystalline cellulose	20.0	20.0	20.0
Modified food corn starch	20.0	20.0	20.0
Lactose	58.5	57.5	34.5
Magnesium Stearate	0.5	0.5	0.5

EXAMPLE 103B Tablets containing 26-100mg of compound

	Amount mg		
Compound of formula (I)	26.0	50.0	100.0
Microcrystalline cellulose	80.0	80.0	80.0
Modified food corn starch	80.0	80.0	80.0
Lactose	213.5	189.5	139.5
Magnesium Stearate	0.5	0.5	0.5

The compound of formula (I), cellulose, lactose and a portion of the corn starch are mixed and granulated with 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active compound per tablet.

EXAMPLE 104 Parenteral injection

	Amount
Compound of formula (I)	1 to 100mg
Citric Acid Monohydrate	0.75mg
Sodium Phosphate	4.5mg
Sodium Chloride	9mg
Water for injection	to 10ml

The sodium phosphate, citric acid monohydrate and sodium chloride are dissolved in a portion of the water. The compound of formula (I) is dissolved or suspended in the solution and made up to volume.

EXAMPLE 105 Topical formulation

	Amount
Compound of formula (I)	1-10g
Emulsifying Wax	30g
Liquid paraffin	20g
White Soft Paraffin	to 100g

The white soft paraffin is heated until molten. The liquid paraffin and emulsifying wax are incorporated and stirred until dissolved. The compound of formula (I) is added and stirring continued until dispersed. The mixture is then cooled until solid.

Example 106A - (Surface-Active Agent) Injection Formulation

Compound of formula (I)	up to 10mg/kg
Tween 80™	up to 2.5%
[in 5% aqueous mannitol (isotonic)]	

The compound of formula (I) is dissolved directly in a solution of the commercially available Tween 80™ (polyoxyethylenesorbitan monooleate) and 5% aqueous mannitol (isotonic).

Example 106B - (Emulsion) Injection Formulation

Compound of formula (I)	up to 30mg/ml
Intralipid™ (10-20%)	

The compound of formula (I) is dissolved directly in the commercially available Intralipid™ (10 or 20%) to form an emulsion.

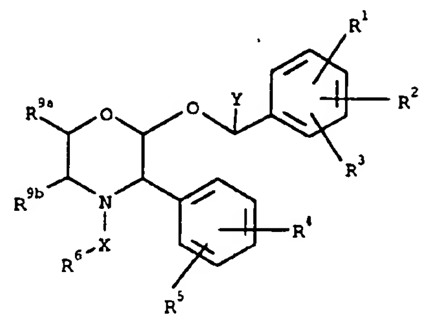
Example 106C - Alternative (Emulsion) Injectable Formulation

	Amount
Compound of formula (I)	0.1 - 10mg
Soybean oil	100mg
Egg Phospholipid	6mg
Glycerol	22mg
Water for injection	to 1ml

All materials are sterilized and pyrogen free. The compound of formula (I) is dissolved in soybean oil. An emulsion is then formed by mixing this solution with the egg phospholipid, glycerol and water. The emulsion is then sealed in sterile vials.

CLAIMS:

1. A compound of the formula (I):



(I)

wherein

R^1 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^2 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^3 is hydrogen, halogen or CF_3;

R^4 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy, CF_3, NO_2, CN, SR^a, SOR^a, SO_2R^a, CO_2R^a, $CONR^aR^b$, C_{2-6}alkenyl, C_{2-6}alkynyl or C_{1-4}alkyl substituted by C_{1-4}alkoxy, where R^a and R^b each independently represent hydrogen or C_{1-4}alkyl;

R^5 is hydrogen, halogen, C_{1-6}alkyl, C_{1-6}alkoxy substituted by C_{1-4}alkoxy or CF_3;

R^6 is a 5-membered or 6-membered heterocyclic ring containing 2 or 3 nitrogen atoms optionally substituted by =O, =S or a C_{1-4}alkyl group, and optionally substituted by a group of the formula ZNR^7R^8 where

Z is C_{1-6}alkylene or C_{3-6}cycloalkylene;

R^7 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by C_{1-4}alkoxy or hydroxyl;

R^8 is hydrogen, C_{1-4}alkyl, C_{3-7}cycloalkyl or C_{3-7}cycloalkylC_{1-4}alkyl, or C_{2-4}alkyl substituted by one or two substituents selected from C_{1-4}alkoxy, hydroxyl or a 4, 5 or 6 membered heteroaliphatic ring containing one or two heteroatoms selected from N, O and S;

or R^7, R^8 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms, optionally substituted by one or two groups selected from hydroxy or C_{1-4}alkyl optionally substituted by a C_{1-4}alkoxy or hydroxyl group, and optionally containing a double bond, which ring may optionally contain an oxygen or sulphur ring atom, a group S(O) or $S(O)_2$ or a second nitrogen atom which will be part of a NH or NR^c moiety where R^c is C_{1-4}alkyl optionally substituted by hydroxy or C_{1-4}alkoxy;

or R^7, R^8 and the nitrogen atom to which they are attached form a non-aromatic azabicyclic ring system of 6 to 12 ring atoms;

or Z, R^7 and the nitrogen atom to which they are attached form a heteroaliphatic ring of 4 to 7 ring atoms which may optionally contain an oxygen ring atom;

R^{9a} and R^{9b} are each independently hydrogen or C_{1-4}alkyl, or R^{9a} and R^{9b} are joined so, together with the carbon atoms to which they are attached, there is formed a C_{5-7} ring;

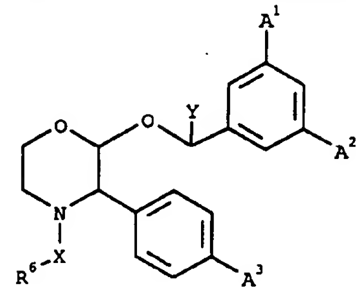
X is an alkylene chain of 1 to 4 carbon atoms optionally substituted by oxo; and

Y is a C_{1-4}alkyl group optionally substituted by a hydroxyl group;

with the proviso that if Y is C_{1-4}alkyl, R^6 is substituted at least by a group of formula ZNR^7R^8 as defined above;

or a pharmaceutically acceptable salt or prodrug thereof.

2. A compound as claimed in claim 1 of formula (Ia):



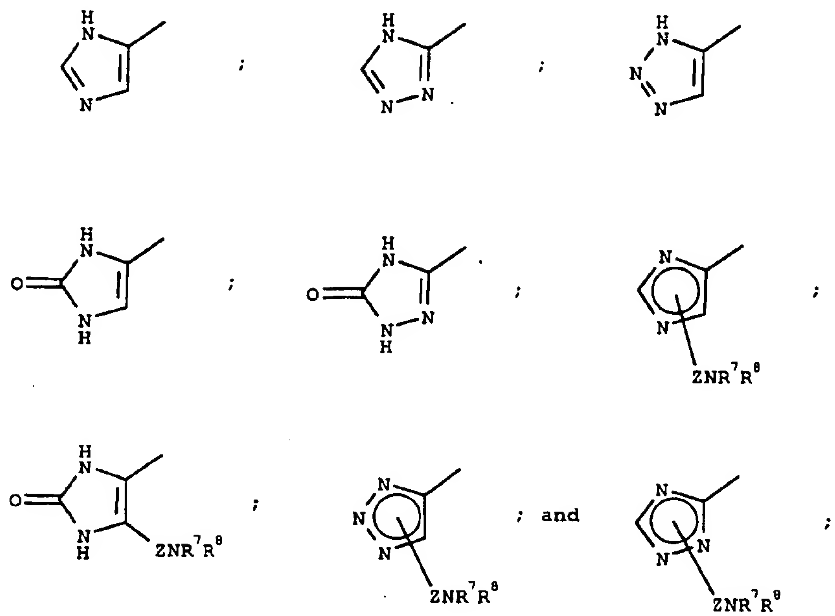
(Ia)

wherein A^1 is fluorine or CF_3;
A^2 is fluorine or CF_3;
A^3 is fluorine or hydrogen;
and X, Y and R^6 are as defined in claim 1;
or a pharmaceutically acceptable salt or prodrug thereof.

3. A compound as claimed in claim 1 or claim 2 wherein Y represents a C_{1-4}alkyl group substituted by a hydroxy group; or a pharmaceutically acceptable salt or prodrug thereof.

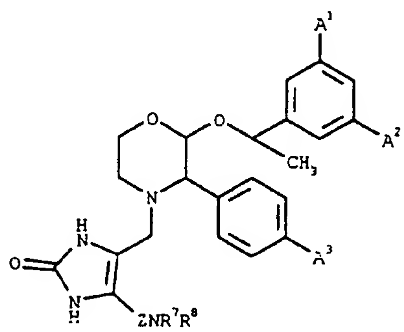
4. A compound as claimed in claim 1 or claim 2 wherein Y represents a C_{1-4}alkyl group, with the proviso that R^6 is substituted at least by a group of the formula ZNR^7R^8 as defined in claim 1; or a pharmaceutically acceptable salt or prodrug thereof.

5. A compound as claimed in any one of claims 1 to 4 wherein R^6 represents a heterocyclic ring selected from:



or a pharmaceutically acceptable salt or prodrug thereof.

6. A compound as claimed in claim1 or claim 2 of formula (Ib):

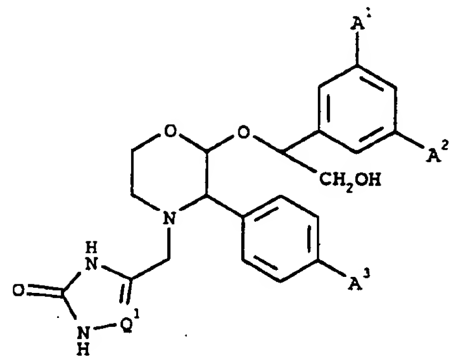


(Ib)

wherein A^1, A^2 and A^3 are defined in claim 2 and wherein Z, R^7 and R^8 are as defined in claim 1;

or a pharmaceutically acceptable salt or prodrug thereof.

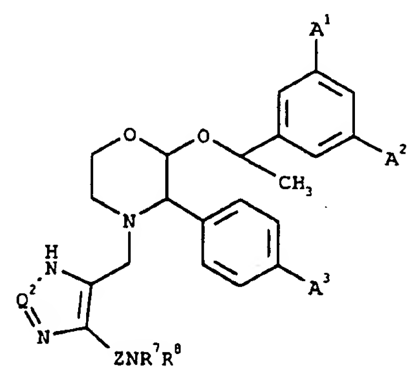
7. A compound as claimed in claim 1 or claim 2 of formula (Ic):



(Ic)

wherein A^1, A^2 and A^3 are as defined in claim 2 and Q^1 is CH, N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in claim 1;
or a pharmaceutically acceptable salt or prodrug thereof.

8. A compound as claimed in claim 1 or claim 2 of formula (Id):



(Id).

wherein A^1, A^2 and A^3 are defined in claim 1, Q^2 is CH or N and Z, R^7 and R^8 are as defined in claim 1;
or a pharmaceutically acceptable salt or prodrug thereof.

9. A compound selected from:

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2,3-dihydro-5-(N,N-dimethylamino)methyl-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

4-(2,3-dihydro-5-(N,N-dimethylamino)methyl-2-oxo-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)morpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(4-hydroxypiperidino)methyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(2,3-dihydro-5-morpholinomethyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-morpholinomethyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

4-(5-azetidinylmethyl-2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(N-methylpiperazinyl)methyl-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-5-(N-(2-morpholinoethyl)aminomethyl)-2-oxo-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-2-oxo-5-(N-(2-pyrrolidinoethyl)aminomethyl)-1,3-imidazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(dimethylamino) methyl-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(N-(N'-methylaminoethyl)-1,2,4-triazol-3-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(N-methylaminomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-aminomethyl)-1,2,3-triazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-pyrrolidinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-(azetidinylmethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl)ethoxy)morpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(5-(pyrrolidinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-fluoro-5-(trifluoromethyl)phenyl) ethoxy)-4-(5-(morpholinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-(N,N-dimethylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(R)-(3-(trifluoromethyl)phenyl)ethoxy)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(N'-methylpiperazinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-(1-(2-pyrrolidinoethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-phenyl-4-(2-(2-pyrrolidinoethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(morpholinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

4-(5-azetidinylmethyl)-1,2,3-triazol-4-yl)methyl-2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-3-(S)-(4-fluorophenyl)-4-(5-(pyrrolinomethyl)-1,2,3-triazol-4-yl)methylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(bis(methoxyethyl)aminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(2-chloro-5-morpholinomethyl-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl)morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,3-imidazol-4-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N,N-dimethylaminomethyl)-1,2,4-triazol-3-yl)methyl-3-(S)-(4-fluorophenyl) morpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N-(2,2-dimethoxyethyl)-N-methylaminomethyl)-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-(2-methoxyethyl)-N-methyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

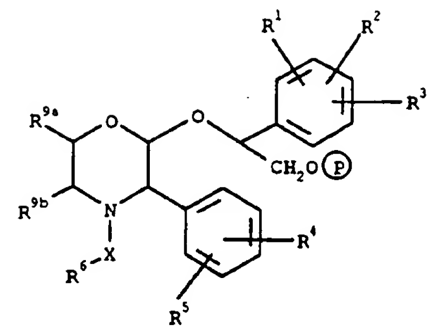
2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-isopropyl-N-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-(N-cyclopropyl-N-(2-methoxyethyl)aminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N,N-dibutylaminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;

2-(R)-(1-(R)-(3,5-bis(trifluoromethyl)phenyl)ethoxy)-4-(5-N,N-diisopropylaminomethyl-1,2,3-triazol-4-yl)methyl-3-(S)-phenylmorpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;
4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-(4-fluorophenyl)-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;
4-(2,3-dihydro-2-oxo-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl) morpholine;
4-(2,3-dihydro-2-oxo-5-pyrrolidinomethyl-1,3-imidazol-4-yl)methyl-2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-(4-fluorophenyl) morpholine;
4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)-3-(S)-phenyl-2-(R)-(1-(S)-(3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;
4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-(3-fluoro-5-(trifluoromethyl)phenyl)-2-hydroxyethoxy)-3-(S)-phenylmorpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-hydroxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)-3-(S)-phenylmethylmorpholine;
3-(S)-phenyl-4-(1,2,4-triazol-3-yl)-2-(R)-(1-(S)-3-(trifluoromethyl)phenyl)-2-hydroxyethoxy)morpholine;
or a pharmaceutically acceptable salt or prodrug thereof.

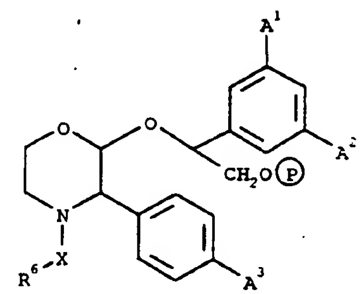
10. A compound as claimed in claim 1 of formula (Ie):



(Ie)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b} and X are as defined in claim 1 and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$;
wherein M^+ is a pharmaceutically acceptable monovalent counterion;
D^{2+} is a pharmaceutically acceptable divalent counterion.

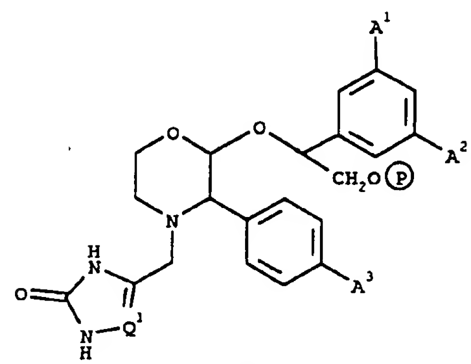
11. A compound as claimed in claim1 or claim 2 of formula (If):



(If)

wherein A^1, A^2 and A^3 are as defined in claim 2, X and R^6 are as defined in claim 1, and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$; wherein M^+ is a pharmaceutically acceptable monovalent counterion; and D^{2+} is a pharmaceutically acceptable divalent counterion.

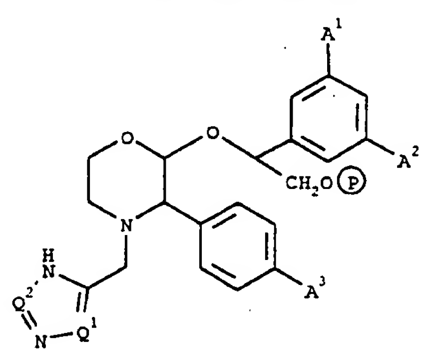
12. A compound as claimed in claim 1 or claim 2 of formula (Ig):



(Ig)

wherein A^1, A^2 and A^3 are as defined in claim 2, Q^1 is CH, N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in claim 1, and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$;
wherein M^+ is a pharmaceutically acceptable monovalent counterion; and D^{2+} is a pharmaceutically acceptable divalent counterion.

13. A compound as claimed in claim 1 or claim 2 of formula (Ih) and pharmaceutically acceptable salts thereof:



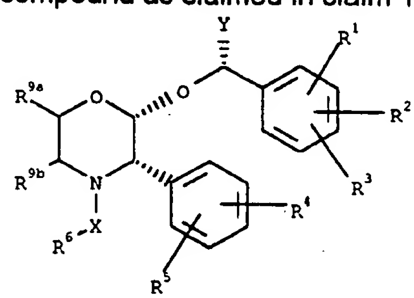
(Ih)

wherein A^1, A^2 and A^3 are as defined in claim 2, Q^1 is CH, N or C-ZNR^7R^8 wherein Z, R^7 and R^8 are as defined in claim 1; Q^2 is CH or N, and P in a circle is $PO(OH)O^-.M^+$, $PO(O^-)_2.2M^+$, or $PO(O^-)_2.D^{2+}$;

wherein M^+ is a pharmaceutically acceptable monovalent counterion; and D^{2+} is a pharmaceutically acceptable divalent counterions.

14. A compound selected from:
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methylmorpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-(4-fluorophenyl)-4-(1,2,4-triazol-3-yl)methylmorpholine;
4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-2-(R)-(1-(S)-3-fluoro-5-(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-3-(S)-phenylmorpholine;
2-(R)-(1-(S)-(3,5-bis(trifluoromethyl)phenyl)-2-phosphoryloxyethoxy)-4-(2,3-dihydro-3-oxo-1,2,4-triazol-5-yl)methyl-3-(S)-phenylmorpholine;
or a pharmaceutically acceptable salt thereof.

15. A compound as claimed in claim 1 of formula (Ii):



(Ii)

wherein R^1, R^2, R^3, R^4, R^5, R^6, R^{9a}, R^{9b}, X and Y are as defined in claim 1; or a pharmaceutically acceptable salt or prodrug thereof.

16. A compound as claimed in any preceding claim for use in therapy.

17. A pharmaceutical composition comprising a compound as claimed in any one of Claims 1 to 15 in association with a pharmaceutically acceptable carrier or excipient.

18. A method for the treatment or prevention of physiological disorders associated with an excess of tachykinins, which method comprises administration to a patient in need thereof of a tachykinin reducing amount of a compound according to Claim 1, or a salt or prodrug thereof, or a composition comprising a compound according to Claim 1, or a salt or prodrug thereof.

19. A method according to Claim 18 for the treatment or prevention of pain or inflammation.

20. A method according to Claim 18 for the treatment or prevention of migraine.

21. A method according to Claim 18 for the treatment or prevention of emesis.

22. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for the treatment of a physiological disorder associated with an excess of tachykinins.

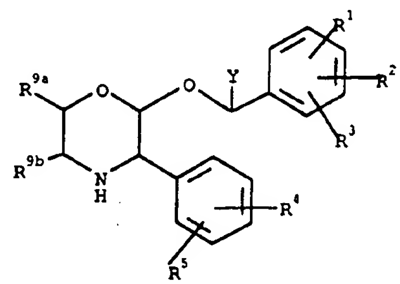
23. The use of a compound as claimed in claim 1 for the manufacture of a medicament for the treatment of pain or inflammation.

24. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for the treatment of migraine.

25. The use of a compound as claimed in Claim 1 for the manufacture of a medicament for the treatment of emesis.

26. A process for the preparation of a compound of formula (I) as claimed in claim 1, which comprises:

(A) reacting a compound of formula (II):



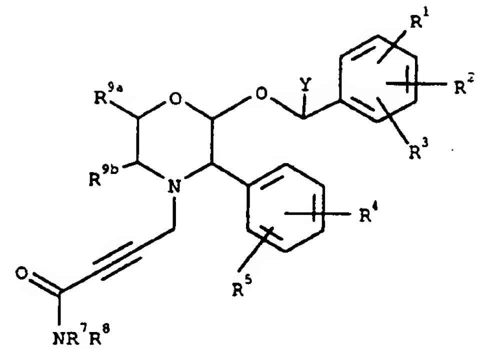
(II)

wherein R^1, R^2, R^3, R^4, R^5 and Y are as defined in relation to formula (I) by reaction with a compound of formula (III):

$$X^1\text{-}X\text{-}R^{6a} \qquad \text{(III)}$$

where X is as defined in claim 1, R^{6a} is a group of the formula R^6 as defined in claim 1 or a precursor therefor and X^1 is a leaving group such as bromine or chlorine; and, if R^{6a} is a precursor group, converting it to a group R^6; or

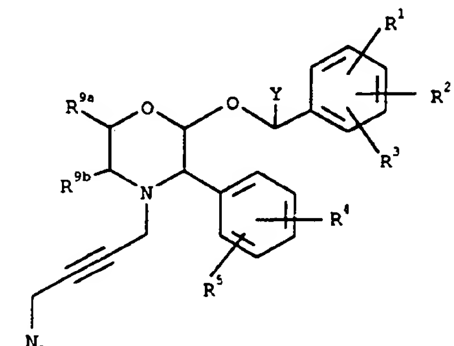
(B) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$ and X is $-CH_2-$, by reaction of a compound of formula (IV)



(IV)

with an azide, followed by reduction of the carbonyl group adjacent to $-NR^7R^8$; or

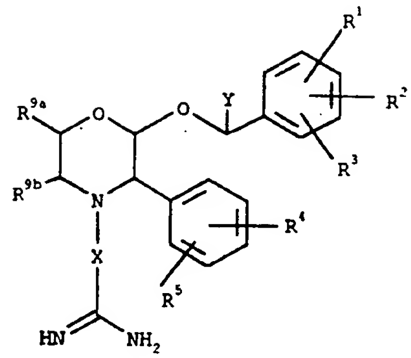
(C) wherein R^6 represents 1,2,3-triazol-4-yl substituted by $CH_2NR^7R^8$ and X is $-CH_2-$, by reaction of a compound of formula (V)



(V)

with an amine of formula NHR^7R^8; or

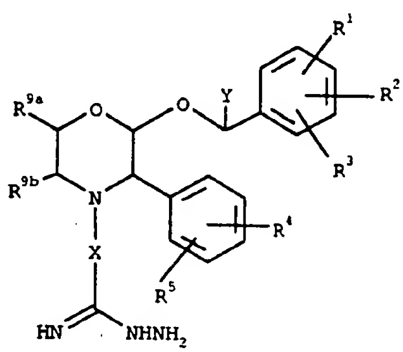
(D) wherein R^6 represents substituted or unsubstituted 1,3,5-triazine, by reaction of compounds of formula (VI):



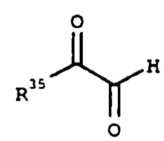
(VI)

with substituted or unsubstituted 1,3,5-triazine; or

(E) wherein R^6 represents substituted or unsubstituted 1,2,4-triazine, by reaction of a compound of formula (VII) with a dicarbonyl compound of formula (VIII):



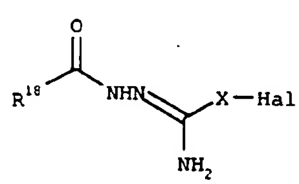
(VII)



(VIII)

wherein R^{35} represents H or a suitable substituent such as ZNR^7R^8; or

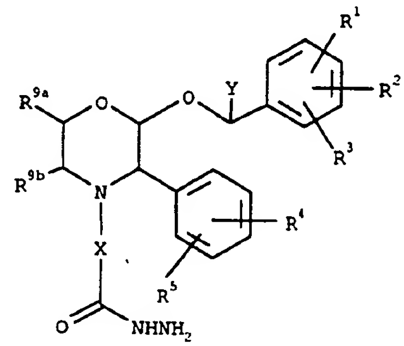
(F) wherein R^6 represents a substituted 1,2,4-triazolyl group, by reaction of a compound of formula (II) with a compound of formula (IX)



(IX)

wherein X is as defined in claim 1, Hal is a halogen atom, and R^{18} is H, $CONH_2$ or OCH_3 (which is converted to an oxo substituent under the reaction conditions), in the presence of a base, followed where necessary by conversion to a compound of formula (I); or

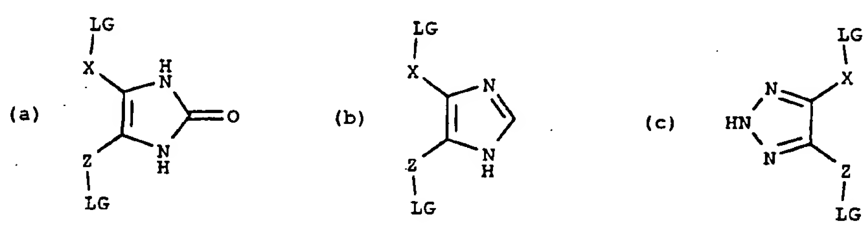
(G) wherein R^6 represents thioxotriazolyl, by reaction of a compound of formula (X)



(X)

with a compound of formula HNCS, in the presence of a base; or

(H) wherein R^6 is substituted by a group of ZNR^7R^8, reacting a compound of formula (XII):



(XII)

wherein each LG, which may be the same or different, is a leaving group, and X and Z are as defined in claim 1, followed by reaction of the resultant compound with an amine NHR^7R^8 to complete the ZNR^7R^8 moiety; or

(J) by interconversion of a compound of formula (I) into another compound of formula (I);

each process being followed, where necessary, by the removal of any protecting group where present;

and when the compound of formula (I) is obtained as a mixture of enantiomers or diastereoisomers, optionally resolving the mixture to obtain the desired enantiomer;

and/or, if desired, converting the resulting compound of formula (I) or a salt thereof, into a pharmaceutically acceptable salt or prodrug thereof.

INTERNATIONAL SEARCH REPORT

Inte. Application No
PCT/GB 94/02819

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D413/06 C07D413/14 C07F9/6533 A61K31/535

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D C07F A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 528 495 (MERCK SHARP & DOHME LTD.) 24 February 1993 see claims	1-26
P,A	EP,A,0 577 394 (MERCK & CO., INC.) 5 January 1994 see examples 17,18,31,36-38,40-43,45,53-56,62 and claims	1-26

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
3 March 1995	22.03.95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Chouly, J

INTERNATIONAL SEARCH REPORT

In[illegible]al application No.
PCT/GB94/02819

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 18-21
because they relate to subject matter not required to be searched by this Authority, namely:
Remark - Although claims 18-21 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Inter. ... Application No
PCT/GB 94/02819

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0528495	24-02-93	AU-A-	2413892	16-03-93
		CA-A-	2112397	04-03-93
		EP-A-	0600952	15-06-94
		WO-A-	9304040	04-03-93
		JP-T-	6510034	10-11-94
EP-A-0577394	05-01-94	AU-B-	4156893	06-01-94
		AU-B-	4656193	24-01-94
		CA-A-	2099233	30-12-93
		CN-A-	1087902	15-06-94
		JP-A-	6172178	21-06-94
		SI-A-	9300346	31-12-93
		WO-A-	9400440	06-01-94
		AU-B-	4160893	06-01-94